Potassium Alkoxides and Thiolates in Transition Metal-Free Synthesis: Mechanism and Application

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Declaration

I, James Cuthbertson, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

…….

Abstract

One of the most significant developments in chemistry over the last forty years has been the ability to harness and exploit the reactivity of low-valent transition metals, especially palladium. A bewildering array of metal and ligand combinations have allowed a similar number of previously unprecedented transformations to become routine; so much so, that transformations such as the Heck, Sonogashira, Suzuki and Stille reactions have become a mainstay of the organic chemist's toolbox. However, the sometimes prohibitive cost of transition metals and ligands, their inherent toxicity and laborious clean up procedures have directed attention towards approaches that bypass the need for transition-metal catalysts.

Recently, a number of publications have indicated that reactions previously thought to be unique to transition metal catalysis could instead occur in the presence of a strong base and a non-metal additive. However, there remains significant controversy regarding the mode of reactivity. This thesis presents evidence to suggest that, under carefully controlled conditions, potassium alkoxides and thiolates have an inherent electron transfer ability. Mechanistic work is presented to suggest that an understanding of this mode of reactivity allows access to a number of substrates and reactions that have previously been considered the preserve of transition metal catalysis, including biaryl formation and *sp*-displacement reactions. In addition, an appreciation of the mode of reactivity of potassium alkoxides has allowed a mechanistic reevaluation of common transformations, such as the synthesis of enol ethers from terminal alkynes. With a solid understanding of the underlying reaction mechanism, the reducing behaviour of cheap and readily available alkoxides or their sulfur analogues could subsequently be applied to the attempted synthesis of chemical scaffolds that are common in many natural products.

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Abbreviations

1,10-phen	1,10-Phenanthroline
AIBN	2,2'-Azobis(2-methylpropionitrile)
Ar	Aryl
Bn	Benzyl
Bu	Butyl
cat.	Catalytic
DFT	Density functional theory
DMEDA	*N*,*N*'-Dimethylethylenediamine
DMF	*N*,*N*-Dimethylformamide
E	Entgegen (opposite)
EPR	Electron paramagnetic resonance
eq	Equivalents
Et	Ethyl
Et_2O	Diethyl ether
GC	Gas chromatography
h	Hours
HRMS	High resolution mass spectrometry
KHMDS	Potassium bis(trimethylsilyl)amide
LDA	Lithium diisopropylamide
LRMS	Low resolution mass spectrometry
LUMO	Lowest unoccupied molecular orbital
m	*Meta*
M	Molar
Me	Methyl
mp	Melting point
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser effect spectroscopy
o	*Ortho*
p	*Para*

PE	Petroleum ether 40 – 60 °C
ppm	Part per million
R	Alkyl
RCM	Ring closing metathesis
rt	Room temperature
SET	Single electron transfer
$S_{RN}1$	Unimolecular radical nucleophilic substitution
TBAF	Tetra-*n*-butylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TEMPO	2,2,6,6-Tetramethylpiperidinyloxy
tert	Tertiary
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	*N*,*N*,*N*',*N*'-Tetramethylethylenediamine
Tol	Toluene
Ts	Tosyl
UV	Ultraviolet
Z	Zusammen (together)

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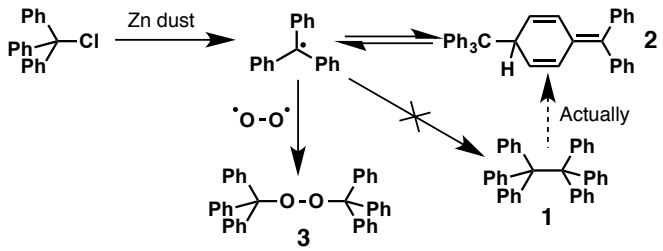
Introduction

1. Radical Chemistry

An appreciation of radical chemistry is of central importance to understanding and improving fundamental chemical transformations, and assembling complex molecules. Previously dismissed as producing highly reactive intermediates, invariably leading to poor selectivity and polymeric tars, radical chemistry has today become a vast and ever expanding field. As such, radical mechanisms are now recognised and studied in almost all disciplines of chemical transformation. For instance, radical intermediates play crucial roles in atmospheric chemistry, polymerisation, organic synthesis, and many biochemical pathways.

1.1. Radical Chemistry – A Brief Introduction

Although the term 'radical' was initially used by Lavoisier in 1789 in describing acids as being composed of oxygen and a "radical", it was the pioneering work of Moses Gomberg[1] in 1900 that provided the first convincing evidence of the existence of these species, and which ushered in a new category of previously unknown chemical species. In studying the reaction of triphenylmethyl chloride with zinc dust in the absence of oxygen, Gomberg reportedly synthesised hexaphenylethane **1** (though this was subsequently shown to have the structure **2**). In the presence of oxygen, peroxide **3** was synthesised, both products indicating the presence of triphenylmethyl radicals (**Scheme 1**).

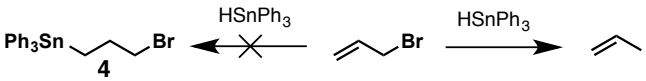


Scheme 1

Whilst the fundamental significance of Gomberg's observations were appreciated at the time, the impact upon mechanistic understanding remained limited, due in part to

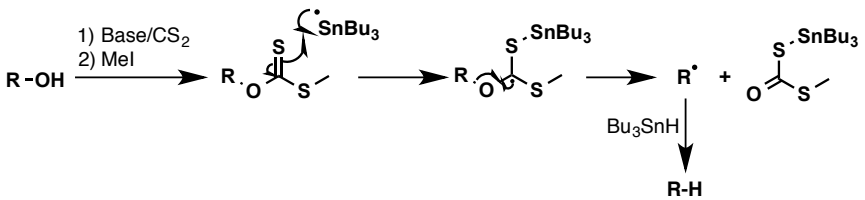
the strength of the ionic theories put forward by Ingold and Robinson in rationalising reaction outcomes. As such, radical-mediated reactions remained an underexplored novelty throughout the early decades of the Twentieth Century.

The drive for synthetic alternatives to natural rubber during the Second World War led to the discovery and understanding of many of the concepts that underpin radical reactions in polymer chemistry, but it was the development of alkyl tin hydrides as radical chain carriers that was responsible for reawakening organic chemists' interest in radical mediated pathways. An unexpected result from van der Kerk and coworkers regarding the attempted hydrostannylation of allyl bromide precipitated this renewed interest.[2] Instead of the expected adduct **4**, the reaction between triphenyltinhydride and allyl bromide produced propene in excellent yield. In the presence of a trace amount of initiator (probably oxygen), bromine abstraction by a tin centred radical occurred, followed by further hydrogen abstraction to complete the chain mechanism (**Scheme 2**).



Scheme 2

This unexpected result initiated a re-emergence of interest in radical chemistry mediated by alkyl tin reagents, epitomised by the Barton-McCombie deoxygenation of alcohols *via* xanthate esters, perhaps the most significant and wide-reaching example (**Scheme 3**).



Scheme 3

Unfortunately, the appetite for alkyltin mediated reactions has been tempered somewhat by the toxicity of the reagent, and the sometimes problematic or laborious product purification and removal of tin residues. Nevertheless, alternative chain

carriers based on organosilicon hydrides or hypophosphites, among others, have been developed to offer reduced toxicity and greater ease of purification.

1.2. Radical Initiation

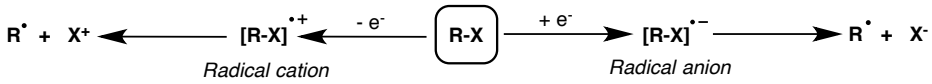
1.2.1. Thermolysis and Photolysis

A general radical chain mechanism consists of initiation, propagation and termination steps. In order to generate radical species, molecules must contain weak covalent bonds, so as to ensure that homolysis of the bond can occur selectively, under relatively mild reaction conditions. The source of energy required to cleave the bond is generally provided thermally or photochemically. For example, heating peroxides to between 50 and 150 °C leads to cleavage of the O-O bond and the generation of two alkoxy radicals, whereas heating azo compounds (eg. AIBN) leads to the cleavage of two C-N bonds, and the release of one equivalent of dinitrogen.

For reactions in which low operating temperatures are necessary, thermolysis is clearly not a viable strategy. In such cases, photoinitiation may be employed. Upon irradiation of a molecule with visible or UV light, absorption and homolysis may occur, a result of the weakening of chemical bonds upon the promotion of electrons to antibonding orbitals of higher energy. Similarly to thermolysis, irradiation of peroxides and azo compounds enables particularly facile access to radical species. In addition, halogens, halides and organometallics may also serve as efficient radical precursors *via* the homolytic cleavage of a weak covalent bond under UV irradiation.

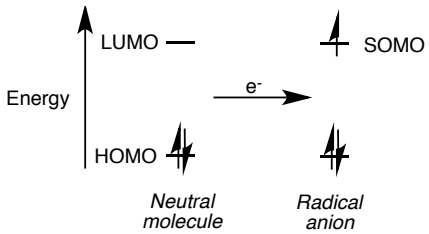
1.2.2. Electron Transfer Mechanisms

Alternatively, redox reactions can be used to access radical species. Radicals are formed upon the transfer of an electron to or from a species that has only paired electrons. Upon the addition of an electron, a radical anion is formed, which may subsequently undergo cleavage to form a radical and an anion (**Scheme 4**, right). When losing an electron, a radical cation is formed, which again may fragment to generate a radical and a cation (**Scheme 4**, left).



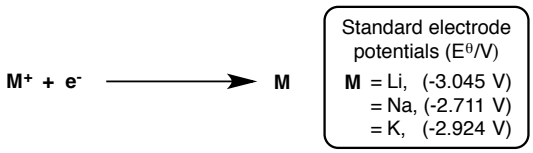
Scheme 4

In terms of the formation of radical anions, the additional electron occupies a low-lying LUMO (**Scheme 5**). With an antibonding orbital occupied, the associated weakening of the structure commonly leads to bond cleavage.



Scheme 5

To form a radical *via* a reduction mechanism, a molecule that is able to donate an electron is required. For this purpose, alkali metals are commonly employed and behave as extremely powerful reducing agents, with loss of an electron yielding a cation that is isoelectronic with noble gases (**Scheme 6**).



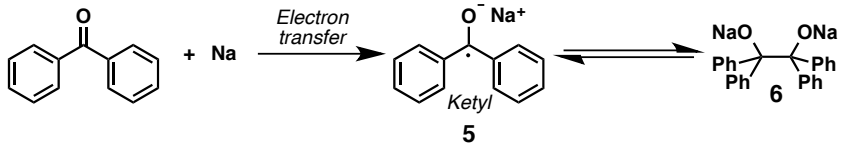
Scheme 6

Typical precursors of radical anions have included aromatics, alkenes and alkynes, carbonyls and halides, due to the presence of a low-lying LUMO into which an electron may be accepted.

1.2.2.1. Carbonyl Reduction

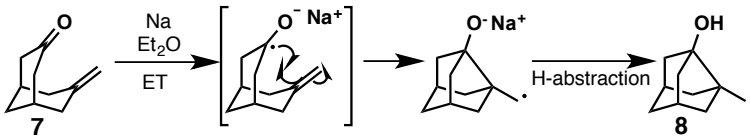
Beckmann and Paul[3] in 1891 were the first to notice the characteristic blue colour upon the addition of sodium to benzophenone in an ethereal solution. Twenty years later and building on this observation, Schlenk and Weickel[4] first suggested that the colour was due to the formation of ketyl radical anion **5**, following electron transfer

from sodium metal (**Scheme 7**). The ketyl radical was found to be in equilibrium with the dimeric species **6**, with the extent of dimerisation dependent upon the nature of the counter cation. It was not until 2000 that Wakatsuki and Hou confirmed the structure of the ketyl radical anion **5** *via* X-ray crystal analysis.[5]



Scheme 7

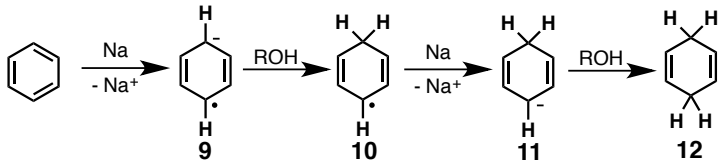
The intermediate ketyl radical may also be intercepted by an olefin, with an overall reductive ring closure observed. An early example of such a transformation was provided by Eakin *et al*. in the reactions of bicyclic systems. Upon single electron reduction of ketone **7** with sodium in non-anhydrous ether, alcohol **8** was obtained as the sole product, arising *via* a *5-exo* cyclisation, subsequent hydrogen atom abstraction from the solvent and protonation (**Scheme 8**).[6]



Scheme 8

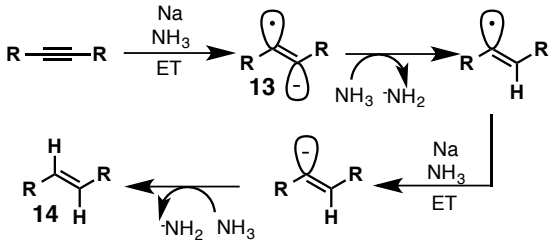
1.2.2.2. Birch Reduction

The use of a single electron transfer mechanism was also exploited by Birch,[7] who in 1944 demonstrated that a solution of sodium in liquid ammonia, in the presence of an alcohol, is able to reduce aromatic compounds to 1,4-cyclohexadienes **12** (**Scheme 9**). The Birch reduction has been extensively employed in synthesis, and now provides excellent access to a variety of reduced aromatic rings and heterocycles. The mechanism, though only speculated upon in the original manuscript, proceeds *via* the transfer of solvated electrons to the aromatic ring, generating a radical anion **9**. The radical anion is protonated in the presence of an alcohol to give a radical **10**, which is reduced to a carbanion **11** by transfer of an electron from a second sodium atom. A final protonation yields the 1,4-cycloheaxadiene product.



Scheme 9

Extension of the solvated electron to internal alkynes by Cambell and Eby[8] led to *E*-alkenes in good yields and a "remarkable state of purity." Again, the mechanism invokes the formation of a radical anion **13**, with the *trans*-geometry a result of the greater stability of the *trans*-alkenyl anion compared to that of the *cis*-isomer. Subsequent protonation, reduction and protonation steps afforded *E*-alkenes **14** (**Scheme 10**).



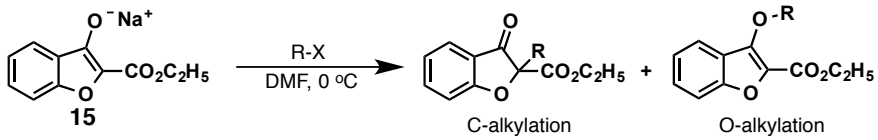
Scheme 10

1.2.2.3. Substitution Reactions and the $S_{RN}1$ Mechanism

In 1966, the groups of both Kornblum[9,10] and Russell[11] independently disclosed experimental evidence that a previously unknown mechanism was in operation for reactions under investigation. Kornblum *et al*. studied the reaction between the sodium salt of *β*-ketoester **15** and nitrobenzyl halides, and observed an unusually high degree of carbon-alkylation for *p*-nitrobenzyl halide (**Table 1**).

The ratio of *C*/*O*-alkylation remains approximately constant for each halide for benzyl- and *meta*-nitrobenzyl halides (**Table 1**, **Entries 1**–**6**), and iodo and bromo *para*-nitrobenzyl halides (**Table 1**, **Entries 8** and **9**). In these instances, alkylation of **15** has been ascribed to an S_N2 process. However, in the case of *para*-nitrobenzylchloride, with a relatively poor leaving group and nitro group in the *para*-position, a different mechanism becomes dominant. A significant increase in the proportion of *C*-alkylated product is accompanied by a large increase in rate upon employing *p*-nitrobenzyl chloride, when compared to previous chlorides. A similar

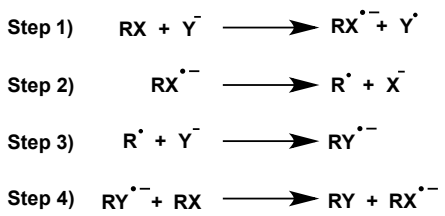
mechanism was observed by Russell in work concerning the coupling of 2-nitro-2-propyl anions and *para*-nitrobenzyl chloride. The mechanism, which proceeds *via* radical intermediates, was identified as the $S_{RN}1$ pathway.



Entry	R-X	C-alkylation (%)	O-alkylation (%)
1	Benzyl-Cl	40	50
2	Benzyl-Br	64	29
3	Benzyl-I	72	18
4	*m*-nitrobenzyl-Cl	40	52
5	*m*-nitrobenzyl-Br	65	28
6	*m*-nitrobenzyl-I	73	18
7	*p*-nitrobenzyl-Cl	**90**	**2**
8	*p*-nitrobenzyl-Br	66	24
9	*p*-nitrobenzyl-I	74	19

Table 1

The $S_{RN}1$ mechanism, or unimolecular radical nucleophilic substitution, involves the nucleophilic, *ipso*-substitution of a species bearing a suitable leaving group. The general mechanistic pathway is outlined in **Scheme 11**.

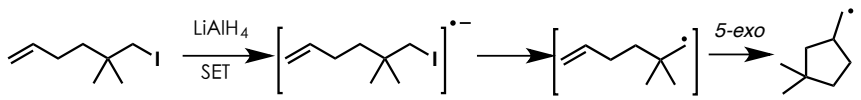


Scheme 11

The $S_{RN}1$ mechanism is a chain process, proceeding *via* intermediate radicals and radical anions. An initial single electron transfer (SET) from the nucleophile (Y^-) to substrate RX generates a radical anion and radical (Step 1). Rapid dissociation of the

radical anion generates a radical ($R^{\cdot}$) and anion (X^-) (Step 2). Alternatively, steps 1 and 2 may be combined in a concerted-dissociative pathway, with the R-X bond broken during electron transfer.[12] In Step 3, the radical reacts with nucleophile Y^- to generate a radical anion, which is then able to transfer an electron to another molecule of substrate RX to maintain the radical chain (Step 4). The $S_{RN}1$ mechanism describes only one of the possible fates of the radical $R^{\cdot}$. Nevertheless, the SET pathway was, until the mid 1970s, considered an anomaly, restricted to a very specific set of reaction conditions and reagents.

Extending the work of Kornblum and Russell, Ashby and coworkers[13,14,15,16] have attempted to show *via* the use of EPR spectroscopy and cyclisable probes that, instead of being applicable to only a small number of processes, SET processes are ubiquitous in organic chemistry. This view has been echoed by Pross, who has presented evidence to suggest that many organic chemistry reactions are better understood in terms of a single electron transfer, rather than a two electron polar mechanism.[17] Ashby *et al*. have provided evidence to suggest that a single electron transfer mechanism is operative in, amongst others, the reactions of 1) Grignard reagents with ketones,[13] 2) reduction of ketones in the presence of alkoxides,[15] 3) reactions of nucleophiles with alkyl halides,[14] and 4) reactions of alkyl halides with $LiAlH_4$ (**Scheme 12**).[16]

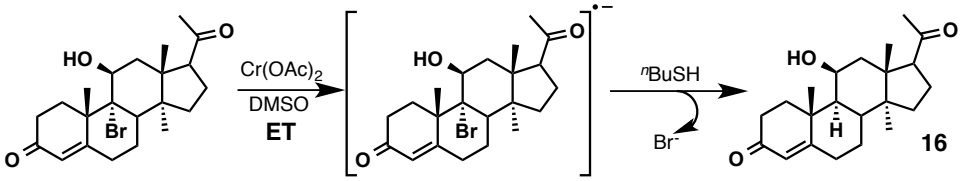


Scheme 12

At the same time, however, the authors highlight the difficulty in determining the contribution made by SET pathways to a given reaction outcome, due in part to discreet changes in reaction mechanism depending on the substrates used and their respective reduction potentials. For instance, in the reduction of carbonyls by alkoxides to form ketyl intermediates, the ketone must be substituted by an aromatic group. Further, in the reaction of nucleophiles with alkyl halides, differences in reaction mechanism are expected upon changing from iodide to chloride leaving groups (**Table 1**).

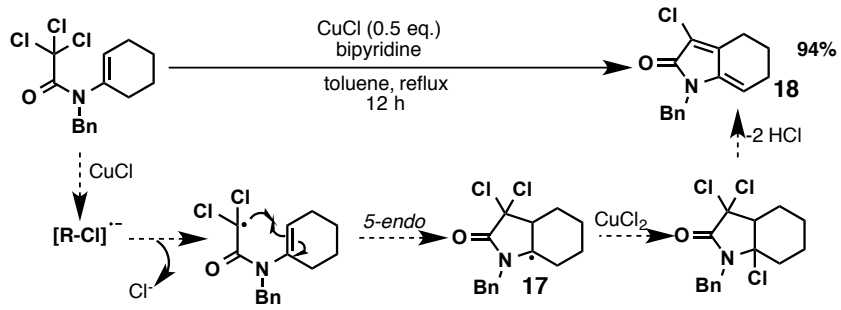
1.2.2.4. Alternative Sources of Reducing Power

Although Group 1 metals are a commonly used source of reducing power in electron transfer reactions, numerous low-valent transition metals have also been routinely employed. For example, chromium(II) and titanium(III) salts have been extensively investigated, and behave as strong reducing agents. For instance, Barton *et al.* employed chromous acetate as the source of reducing power in the synthesis of 11β-hydroxy steroids **16** (**Scheme 13**).[18] Initial electron transfer from the metal salt generates a radical anion, with subsequent fragmentation generating a radical and bromide ion. Hydrogen abstraction from a thiol generates the reduced species, allowing selective removal of the halide in the presence of the 11β-hydroxy group.



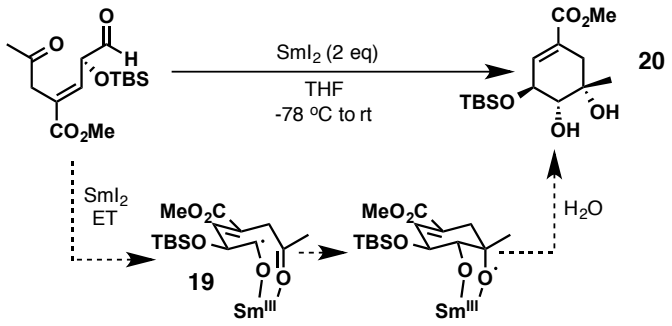
Scheme 13

Iron(II) and copper(I) salts have also been employed as single electron reducing agents, though they are significantly milder than titanium and chromium salts. As such, they are generally unable to reduce carbonyls or alkyl halides, but are able to readily reduce peroxides, hydroperoxides, diazonium salts and certain polyhalogenated substrates. For instance, Davies *et al.*[19] have employed copper(I) chloride to access pyrrolidinones **18**. Addition of bipyridine serves to coordinate and solubilise the copper(I) chloride. An initial electron transfer is followed by cleavage of the C-Cl bond, then an unusual 5-*endo* cyclisation, originally described by Ikeda and Ishibashi.[20] Quenching of the resulting radical **17** with chlorine, and loss of two equivalents of HCl gave access to substituted pyrrolidinones **18** in excellent yield (**Scheme 14**).



Scheme 14

Samarium diiodide has proven to be an extremely versatile and powerful source of reducing power. Particularly exploited in electron transfer to carbonyls and subsequent pinacol couplings, the oxygen atom of an initially formed ketyl radical forms a complex with samarium (**19**), often leading to products that exhibit excellent stereocontrol. Reactions are generally extremely rapid and clean. For example, Hanessian *et al*.[21] employed samarium diiodide in the synthesis of cyclic vicinal *cis*-diols (**20**) *via* a pinacol coupling reaction (**Scheme 15**).



Scheme 15

Far from leading solely to highly reactive intermediates and unpredictable reactions, the identification and exploitation of radical chemistry has led to the emergence of an extremely broad reactivity profile, with selectivity often complimentary to that exhibited by ionic mechanisms. Many reactions believed to exemplify ionic processes (e.g. S_N2 displacements) have been suggested to proceed, at a very minimum, with a contribution from a radical mechanism,[14] with single electron transfer thought to be crucial to the initiation of reactivity. The identification of reaction mechanisms that may proceed *via* a mechanism that is initiated by electron transfer is therefore important both from the point of fundamental understanding of reactivity, and in the design of efficient chemical transformations.

2. Biaryl Synthesis

The biaryl motif has long been regarded as a synthetically attractive template, due in part to its presence in the structures of many pharmaceutical compounds and biologically active molecules (**Figure 1**). For instance, the biaryl subunit is present in *Valsartan*, *Telmisartan* and *Losartan*, each used in the treatment of hypertension.[22,23,24]

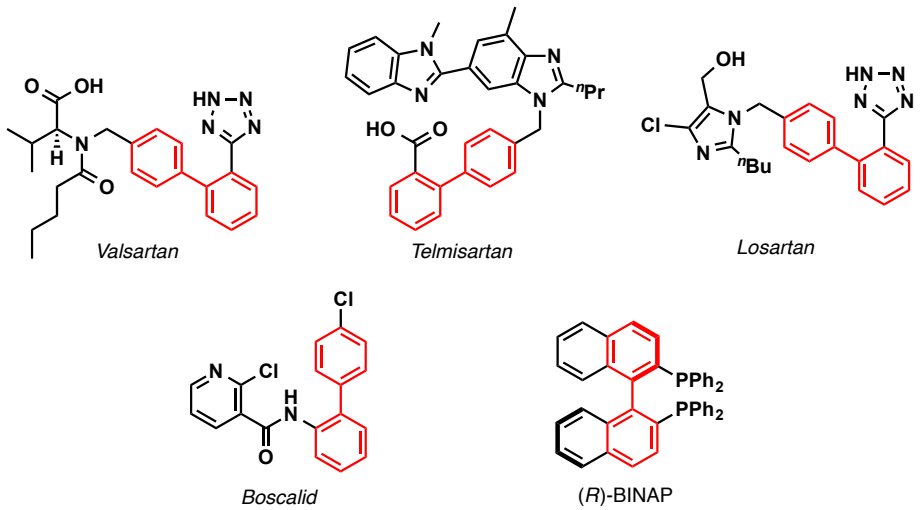


Figure 1

The biaryl motif has also found use in polymers, dyes and agrochemicals such as the fungicide *Boscalid*.[25] In addition, biaryl-containing units such as binap can exhibit restricted axial rotation, and so impart chirality in a reaction.[26] In light of this significance, research into the construction of biaryls has spanned over a century of work, and has undergone several significant and discreet changes in approach.

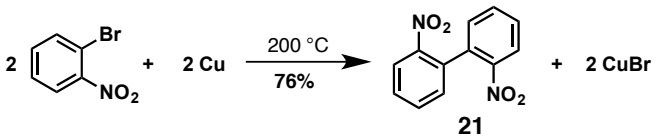
2.1. Biaryl Synthesis – A Brief History

The ability to selectively form carbon-carbon bonds is one of the fundamental goals in organic synthesis. The breadth of approaches employed towards realising this objective is well demonstrated within the history of biaryl synthesis. Transition metal mediated/catalysed approaches towards biaryl units have been studied since the turn of the 20th Century, and represent a continually evolving area of research. Approaches towards biaryls under transition metal mediation can generally be grouped into; 1) homocoupling Ullmann-type reactions requiring the use of stoichiometric metal

reagents; 2) transition metal catalysed cross-coupling between electrophiles and nucleophiles; 3) direct C-H activation reactions.

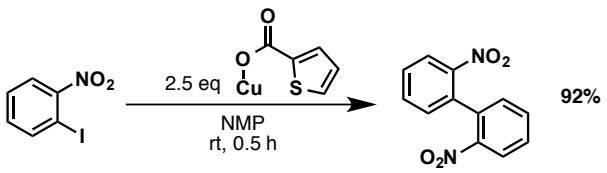
2.1.1. Ullmann-Type Homocoupling

Early approaches towards biaryls from monoaryl precursors were reliant upon the use of stoichiometric transition metal reagents. Ullmann and Bielecki showed in 1901 that dinitrobiphenyl molecules **21** could be formed in 76% yield simply by heating bromonitrobenzene in the presence of copper at high temperatures (≥ 200 °C), (**Scheme 16**).[27]



Scheme 16

The reaction proceeds *via* an intermediate cuprate, and a copper halide is formed as a byproduct. Though representing a significant step forward in terms of carbon-carbon bond formation, the eponymous Ullmann reaction is clearly restricted by the need for high temperatures and the use of stoichiometric amounts of copper, and is limited to the synthesis of symmetrical biaryls. Later modifications, such as Liebskind's use of a readily available, air stable thiophene carboxylate reagent, allow coupling to proceed at ambient temperatures (**Scheme 17**).[28]



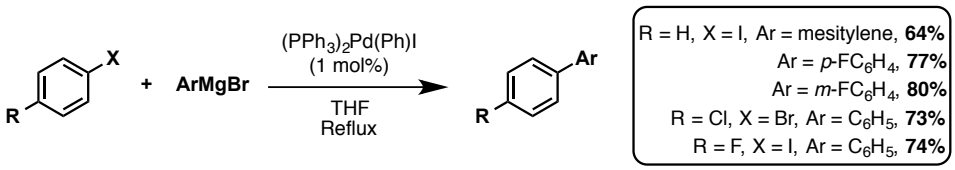
Scheme 17

2.1.2. Transition Metal Catalysed Cross-Coupling

Subsequent transition metal catalysed approaches to the synthesis of biaryls have generally relied upon the use of a prefunctionalised organometallic in combination with an aryl halide (or other pseudohalide leaving group, such as triflate). Although many metals have been used catalytically to promote biaryl formation, the significant

step forward came in the mid 1970s, with the use of palladium and nickel catalysis allowing access to a considerably expanded variety of biaryl structures.

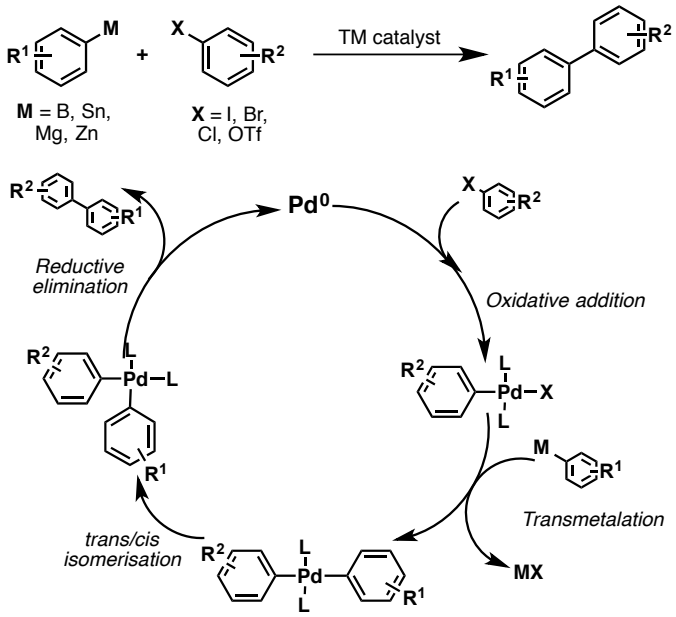
Building on initial work conducted by Kharasch,[29] Ishikawa and Sekiya[30] showed that the cross-coupling of aryl bromides and iodides with aryl Grignard reagents was considerably more efficient upon inclusion of the catalyst $(PPh_3)_2Pd(Ph)I$. Importantly, inclusion of the catalyst ensured that the use of Grignard reagents no longer limited the reaction to homocoupled products, with the aryl halide acting as the cross-coupling partner (**Scheme 18**).



Scheme 18

Clearly however, the continued use of a Grignard reagent precludes application to cross-coupling partners that contain, for example, carbonyl or nitro functional groups.

By altering the nature of the prefunctionalised unit, the use of palladium as catalyst has allowed chemists to circumvent many of the functional group tolerance problems associated with the use of Grignard reagents. Now forming standard techniques in the synthetic chemist's toolbox, the Negishi,[31] Suzuki[32] and Stille[33] reactions first appeared in the mid-1970s, and revolutionised transition metal catalysed cross-coupling, allowing access to a bewildering range and complexity of biaryl containing products. Indeed, the importance of these reactions has been acknowledged by the award of the 2010 Nobel Prize in Chemistry jointly to Negishi and Suzuki (and Heck) for, "palladium-catalyzed cross-couplings in organic synthesis."[34]



Scheme 19

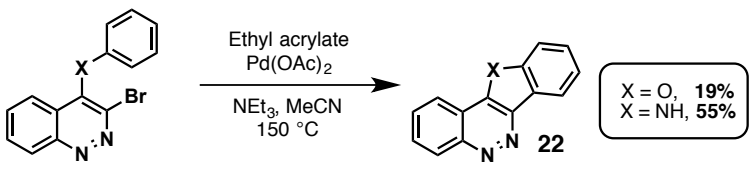
Most palladium-catalysed cross-coupling reactions are proposed to follow a broadly similar catalytic cycle, constituting oxidative addition, transmetallation, isomerisation and reductive elimination steps (**Scheme 19**). The Negishi reaction makes use of organozinc compounds as coupling partners, and was the first reaction to allow the synthesis of unsymmetrical biaryls in good yields. The use of the less-reactive organozinc compounds negates many of the functional group compatibility problems associated with the use of Grignard reagents, allowing access to a considerably broader array of biaryls. However, the organozincs used are moisture and air sensitive, a particular hinderance when compared to the Suzuki and Stille reactions.

The use of organostannanes and boronic acids as coupling partners ushered in the Stille and Suzuki reactions respectively. Both tolerate an extremely wide range of functional groups with varying electronic characters, and are not moisture and air sensitive, a considerable advantage over the Negishi reaction. The Stille reaction has the advantage of being conducted under neutral conditions, increasing functional group tolerance relative to the Suzuki procedure. Whilst boronic acids show low toxicity, the main drawback of the Stille reaction is the toxicity of the organotin reagents. Nevertheless, these three reactions allowed chemists access to an unprecedented array of previously inaccessible structures.

2.1.3. Synthesis of Biaryls *via* C-H Activation

Despite the obvious benefits provided by the Negishi, Stille and Suzuki reactions, the requirement for prefunctionalisation with an electropositive group often requires extending a synthetic procedure by several steps. In addition, many transition metals and associated ligands are extremely expensive, and toxic to different extents, and so the rigorous purification required can be challenging. Costs associated with additional reagents, purification and possible side products inevitably follow. Procedures in which prefunctionalisation is unnecessary, and which proceed *via* the direct functionalisation of an unactivated C-H bond are therefore highly desirable. Although any substitution of a C-H bond can be thought to have involved a C-H activation step at some point in the reaction profile, in this instance the term is used to refer to direct arylation reactions, in which a prefunctionalised organometallic is replaced by an unfunctionalised arene. However, this transformation is limited by the relative inertness of unactivated C-H bonds (the dimerisation of benzene is unfavourable by 13.8 kJ/mol, and only gives appreciable yields of biphenyl at drastic temperatures of ~800 °C [35]), and the ubiquity of C-H bonds in synthesis, making regioselectivity prohibitively difficult.

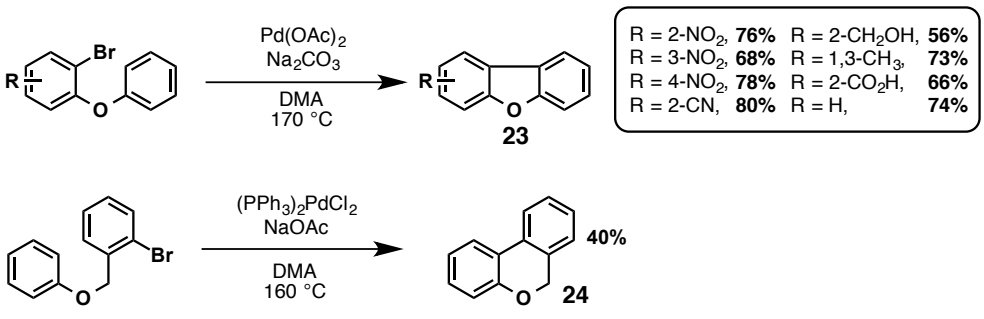
Despite this, several groups have managed to achieve direct arylation of C-H bonds, both *intra*- and *inter*molecularly. Although early successes required the use of stoichiometric amounts of a palladium catalyst,[36] one of the first examples of a catalytic *intra*molecular direct C-H functionalisation came from the group of Ames *et al.*[37] during an attempted Heck reaction (**Scheme 20**). None of the expected Heck type product was isolated, with **22** instead isolated following a dehydrobromination reaction.



Scheme 20

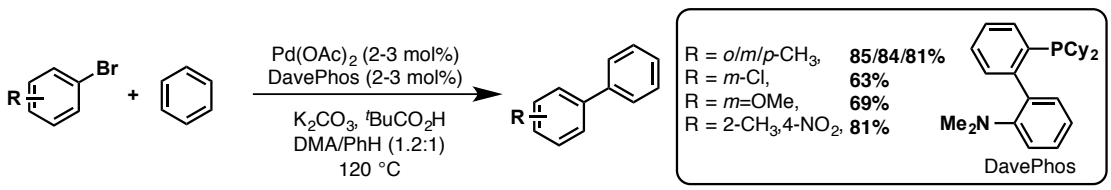
Further investigations allowed unprecedented access to benzofurans[38] **23** and benzopyrans[39] **24**, albeit in moderate yields for the six-membered rings. The reaction

was tolerant of electron donating and withdrawing groups, giving access to benzofurans in good yields (**Scheme 21**), although there is no indication that control reactions were conducted to confirm the necessity of palladium.



Scheme 21

*Inter*molecular arylations *via* C-H activation generally require electron rich substrates such as indoles, thiophenes and furans,[40,41] or the use of an *ortho*-directing group to both control the regioselectivity and hold the aromatic ring within the coordination sphere of the metal.[42] Whilst examples of palladium-catalysed arylation of unactivated benzene are few, Fagnou *et al*.[43] have been instrumental in expanding the reaction to unactivated aromatics. The inclusion of a pivalic acid-palladium combination catalyst allows biaryl coupling of benzene and aryl bromides to proceed with excellent scope and yields (**Scheme 22**). Interestingly, aryl iodides and chlorides both show significantly diminished reactivity when compared to bromides.

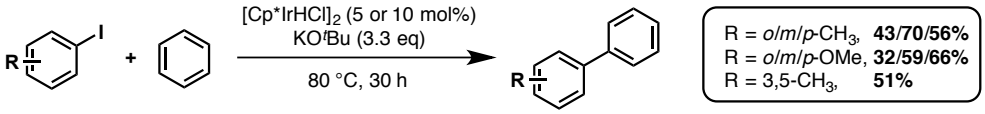


Scheme 22

2.1.4. Biaryl Synthesis *via* Radical Intermediates

An alternative, aryl-radical mediated mechanism has been invoked in the synthesis of biaryls *via* direct C-H functionalisation. In the presence of a catalytic amount of an iridium complex and potassium *tert*-butoxide, Yamaguchi *et. al.*[44] have shown that

coupling occurs between unactivated benzene and aryl iodides to yield biaryls in reasonable yields (**Scheme 23**). The intermediacy of an aryl radical was inferred from the observed high *ortho*-selectivity upon arylation of anisole and toluene. Previous procedures that have invoked a radical mechanism generally require a stoichiometric amount of a radical initiator, clearly demonstrating the power of the iridium catalysed procedure, though the extremely long reaction time of 30 hours represents a significant drawback, and raises questions about the necessity of the catalyst.



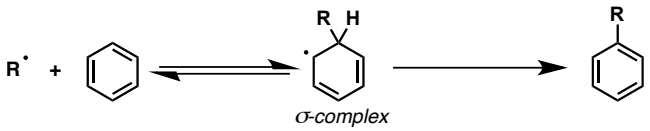
Scheme 23

2.2. Transition Metal-Free Biaryl Synthesis

The term 'transition metal-free' could in theory be applied to all reactions in which an externally added transition metal is not required in the reaction. In reviewing transition metal-free coupling reactions, Shi and Sun[45] have attempted to classify such processes as proceeding *via* one of seven possible discrete pathways.[46] Of these, only those reactions in which a radical pathway proceeding *via* homolytic-aromatic substitution is suspected will be considered here.

2.2.1. Homolytic Aromatic Substitution

Homolytic-aromatic substitution (HAS) has been defined by Williams[47] as reactions, "in which substitution of atoms or groups…attached to aromatic nuclei is effected by free radicals of various kinds." The general transformation is shown in **Scheme 24**.



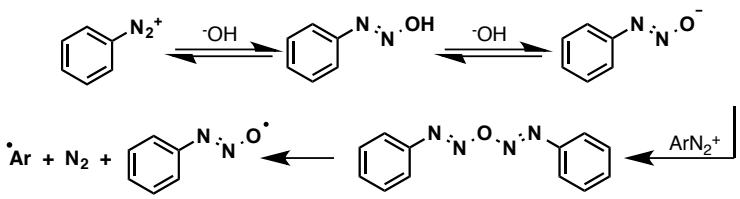
Scheme 24

The addition of a nucleophilic radical to an aromatic ring yields the cyclohexadienyl radical, or σ-complex. Intermediate cyclohexadienyl radicals are then able to

rearomatise *via* a number of possible pathways including disproportionation, hydrogen transfer from an initiator or reaction with further radicals,[48] to generate the homolytic aromatic substitution products. In terms of the synthesis of biaryls, R is an aromatic unit. Numerous generic functionalities have been used as precursors to gain access to aryl radicals, including aromatic diazonium salts, aromatic peroxides and aryl halides.

2.2.2. Diazonium Salts and Aroyl Peroxides

The use of palladium catalysed cross-coupling has, to a large extent, diminished enthusiasm for reactions proceeding *via* aryl radicals in organic synthesis, due in part to poor yields and regioselectivity. In addition, precursors are often difficult to prepare and handle. For instance, diazonium salts have been utilised as aryl radical precursors. By increasing the *p*H of a solution of diazonium salt, aryl radicals are formed and biaryl formation mediated by HAS can occur to yield biaryls *via* the Gomberg-Bachman reaction (**Scheme 25**).[49] Again, yields are generally poor due to the high reactivity of diazonium salts.



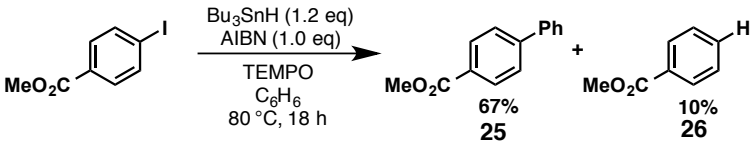
Scheme 25

Aroyl peroxides have also been employed as aryl radical precursors, with cleavage of the O-O bond of benzoyl peroxide occurring upon thermolysis, followed by loss of carbon dioxide to give rise to aryl radicals. In an aromatic solvent, aryl radical addition to the solvent gives rise to biaryls. The inefficient nature of the reaction is exemplified by the low yields observed (typically < 40%) and number of undesired, often inseparable side products.[50]

Although several precursors to aryl radicals therefore exist, the ready availability and ease of handling of aryl halides has led to their emergence as the precursor of choice in homolytic aromatic substitution reactions.

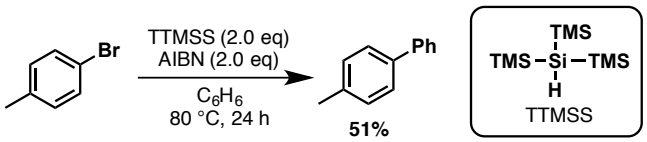
2.2.3. Aryl Radicals *via* Aryl Halides

Aryl halides have generally been used in combination with a stoichiometric amount of a radical chain carrier in order to generate aryl radicals. Bu_3SnH in combination with AIBN has been widely used, for example by Curran *et al*., in the generation of aryl radicals and the subsequent synthesis of biaryls **25**. Reduced products **26** may also be formed upon hydrogen abstraction (**Scheme 26**).[51] As a known radical scavenger, the inclusion of TEMPO in a radical mediated transformation seems unusual. Exploiting the persistent radical effect, TEMPO is postulated to play a role in the rearomatisation of intermediate cyclohexadienyl radicals.



Scheme 26

The use of readily available arylhalides considerably expanded the possible substrates available for the generation of aryl radicals, though the toxicity of organotin reagents when used as chain carrier must also be taken into account. Other commonly used chain carriers have included organosilanes, organoboron derivatives and samarium diiodide. For instance, Builla *et al.*[52] have utilised TTMSS in combination with AIBN as initiator to achieve the *inter*molecular addition of aryl or heteroaryl radicals to the solvent (**Scheme 27**).

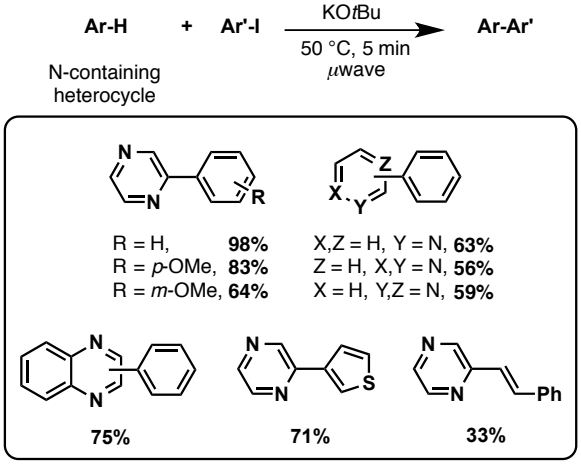


Scheme 27

2.2.4. Biaryl Synthesis from Electron Deficient Heterocycles

An alternative approach towards transition metal-free biaryl cross-coupling using aryl halides was documented in 2008 by Itami *et al.*, and allowed access to biaryls *via* the coupling of electron-deficient nitrogen heterocycles and haloarenes.[53] Discovered fortuitously during the control experiments of an iridium-catalysed process, the

reaction proceeds in the presence of potassium *tert*-butoxide alone, without the need for a transition metal additive. By treating an excess of pyrazine with iodobenzene and potassium *tert*-butoxide under microwave irradiation at 50 °C, a 98% yield of 2-phenylpyrazine was obtained after 5 minutes. The reaction was shown to be applicable to various *N*-containing heterocycles, whilst also tolerating alternative haloarene coupling partners, though proceeded with diminished efficiency with bromobenzenes (**Scheme 28**).



Scheme 28

In addition to the fundamental interest sparked by such a reaction, the work presented several interesting observations that were to become a running theme throughout subsequent transition metal-free processes. For instance, the use of sodium or lithium *tert*-butoxide in place of the potassium salt does not lead to the expected product under the standard conditions, with a temperature in excess of 80 °C instead required for successful NaO^{t}Bu mediated reaction. The reactions occurred exclusively at the halogenated position, with no regioisomers with respect to the iodoarene observed, excluding a benzyne mechanism. A radical mechanism proceeding *via* homolytic aromatic substitution or $S_{RN}1$ was tentatively proposed owing to suppression of the reaction in the presence of TEMPO, though the authors gave no further mechanistic insight.

2.2.5. Phenanthroline and Diamines – A 'Conceptual Breakthrough'

A 'conceptual breakthrough' was heralded with the simultaneous publications from the groups of Shi *et al*.[54], Hayashi and Shirakawa *et al*.[55] and Kwong and Lei *et al*.[56]

Working independently, the three groups demonstrated the direct arylation of unactivated benzene. The reactions all proceed in the presence of potassium *tert*-butoxide and a substoichiometric amount of an additive (or 'ligand'), generally a 1,10-phenanthroline derivative, or a secondary amine such as DMEDA (**Figure 2**).

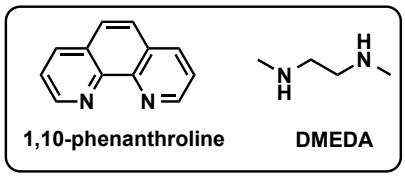
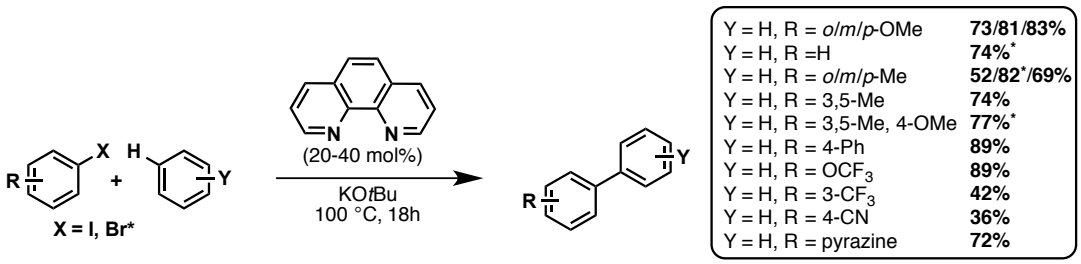


Figure 2

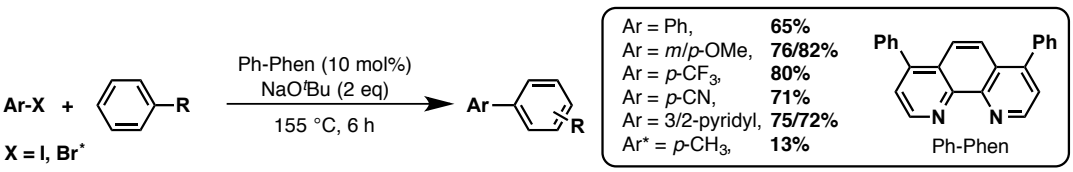
Having again rather fortuitously determined *via* optimisation control experiments that a cobalt catalyst was unnecessary, Shi *et al*. employed 1,10-phenanthroline as their ligand in the coupling of benzene and 4-iodoanisole. The reaction could occur simply in the presence of KO^{t}Bu and 20 mol% 1,10-phenanthroline, giving an 83% isolated yield at 100 °C. The reaction was applicable to electron rich and deficient iodo- and bromoarenes, and different arene coupling partners, considerably widening the scope of reactions compared to the work of Itami, with generally excellent yields (**Scheme 29**). In agreement with Itami, nitrogen containing heterocycles also underwent coupling smoothly with iodobenzene. Mechanistically, the reaction is proposed to proceed *via* the intermediacy of aryl radicals, though the authors provide no further discussion of mechanism.



Scheme 29

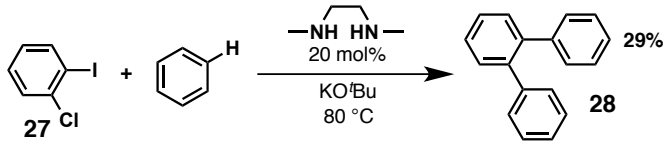
Similarly to Shi, Hayashi *et al*.[55] also employed a phenanthroline derivative as the additive in their biaryl synthesis. The 'ligand' of choice was bathophenanthroline (Ph-Phen), which had also shown increased activity in the work of Shi *et al*. Again, biaryls were formed in good yields, and the reaction tolerated a wide range of functional

groups. Significantly, the authors presented an electron deficient chloride (*p*-CN, 75%) that also underwent the coupling reaction. The authors utilised sodium *tert*-butoxide throughout, though noted there was little difference in efficiency compared to KO^{t}Bu. Lithium *tert*-butoxide showed considerably diminished reactivity (23% conversion, 7% isolated yield under the conditions of **Scheme 30**, R = *p*-CH_3) compared to sodium and potassium analogues. Significantly higher temperatures allow considerably shorter reaction times and lower phenanthroline loading than in the work of Shi *et al.* (**Scheme 29**).



Scheme 30

In a deviation from phenanthroline derivatives, Kwong and Lei *et al.*[56] made use of *N,N'*-dimethylethylenediamine (DMEDA) as the preferred 'ligand', as well as highlighting the similar efficiency of *cis*-cyclohexane-1,2-diol as an additive. Biaryls were again formed in generally excellent yields from iodides, whilst bromides and chlorides in the presence of an iodo group (**27**) could also undergo coupling to give disubstituted products **28**, albeit in low yields (**Scheme 31**).

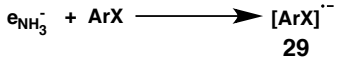


Scheme 31

A significantly milder temperature of 80 °C was required for the coupling, compared to the 155 °C employed by Hayashi. Similarly to Itami *et al.*, the crucial nature of KO^{t}Bu was succinctly demonstrated by the lack of reaction with lithium and sodium analogues. The authors again proposed the intermediacy of a radical species owing to reaction suppression in the presence of TEMPO, though no mechanistic insight beyond a proposed intermediate radical anion was presented.

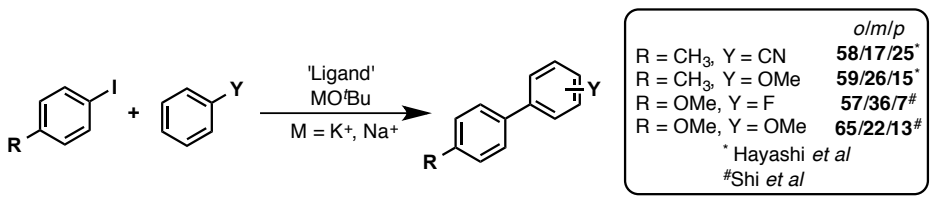
2.2.6. Reaction Mechanism

In each of the Shi, Hayashi and Shirakawa, and Kwong and Lei publications, an intermediate aryl anion is proposed. In describing the mechanism of $S_{RN}1$ reactions, Bunnett[57] has shown that aryl halides are able to act as single electron acceptors, forming radical anions **29** in the presence of electrons solvated in ammonia (**Scheme 32**).



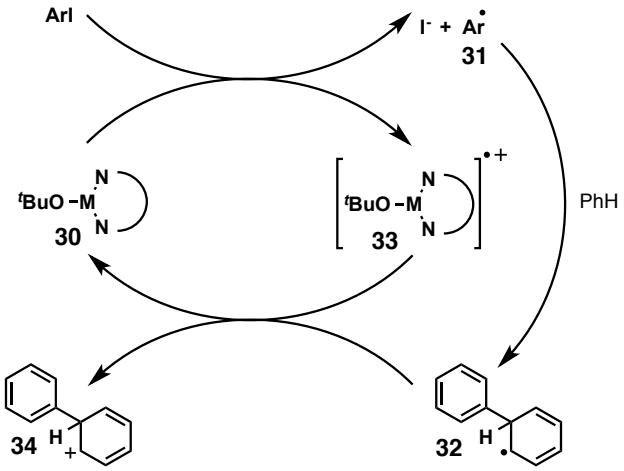
Scheme 32

Cleavage of the haloaryl radical anion hence affords a halide and the proposed aryl anion. The existence of aryl radicals can be inferred from the effect of radical scavengers such as TEMPO (Shi *et al.* and Kwong/Lei *et al.* report a shutdown of the reaction upon addition of radical scavengers) and the requirement for a large concentration of acceptor (benzene is used as solvent, typically ~80 fold excess), both of which are consistent with aryl radical intermediates.[58] In addition, the observed high *ortho*-selectivity when reacting with unsymmetrical aromatic acceptors is typical of aryl radical reactions (**Scheme 33**).[59]



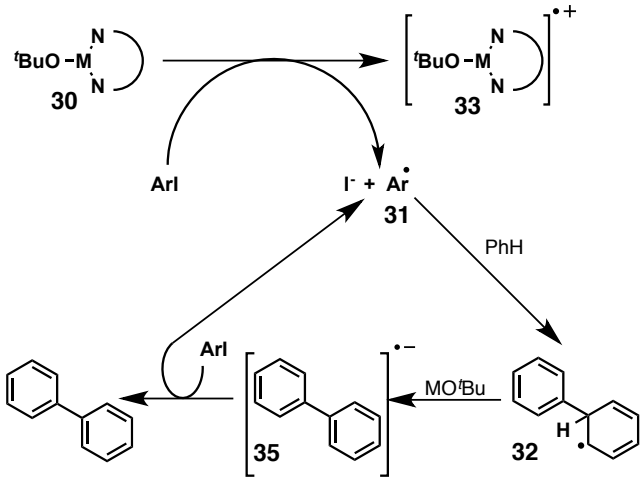
Scheme 33

Hayashi *et al.* have proposed a mechanism for the transformation (**Scheme 34**). Initial association between the metal alkoxide and phenanthroline gives complex **30**. Single electron transfer from **30** to an aryl iodide gives a radical anion (and radical cation **33**), which upon cleavage yields the aryl radical **31** and iodide. **31** can add to benzene to give cyclohexadienyl radical **32**, which is oxidised by **33** to yield cation **34**. Deprotonation subsequently yields the biaryl coupling product.



Scheme 34

Studer and Curran[58] point out that the oxidation of **32** by **33** is inherently unlikely as both are transient species, and that the initial single electron transfer to an aryl iodide is more likely an initiation event than a step in a non-chain process. As the presence of base is crucial, the reaction is a base promoted homolytic aromatic substitution. Studer and Curran also propose that proton transfer from **32** is likely to occur prior to electron transfer owing to the large concentration of base present. As such, a radical anion **35** is formed, which can regain aromaticity *via* electron transfer to a further molecule of aryl iodide. In light of this, a modified mechanism from Hayashi *et al*.[60] has been proposed (**Scheme 35**).



Scheme 35

2.3. The Role of Additives

Despite the widespread use of phenanthroline derivatives, and to a lesser extent diamines, in transition metal-free processes, an understanding of the exact role played by these additives remains under-developed. Whilst there is a general agreement that such transition metal-free coupling reactions proceed *via* the intermediacy of an aryl radical species, the generation of this radical (i.e. the initiation step), and specifically the role played by additives in the initiation has been much speculated upon. Since the original publications of Shi *et al*., Hayashi *et al*., and Kwong and Lei *et al.*, there have been numerous examples of transition metal-free biaryl synthesis, using a seemingly endless variety of additives. Simple alcohols[56,61] (**36**), *N*-heterocyclic carbenes[62] (**37**), zwitterionic radicals[63] (**38**), simple amino acids[64] (**39**), macrocylic pentamers[65] and graphene oxide[66] show the breadth of molecules that have been shown to mediate the transition metal-free synthesis of biaryls (**Figure 3**). However, common to all of these successful couplings is the combination of a strong base (generally KO^{t}Bu) and an additive, and an underlying base-promoted HAS mechanism.

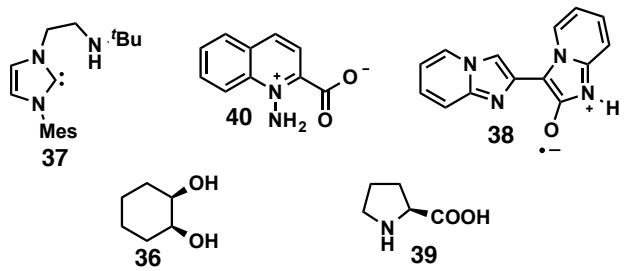


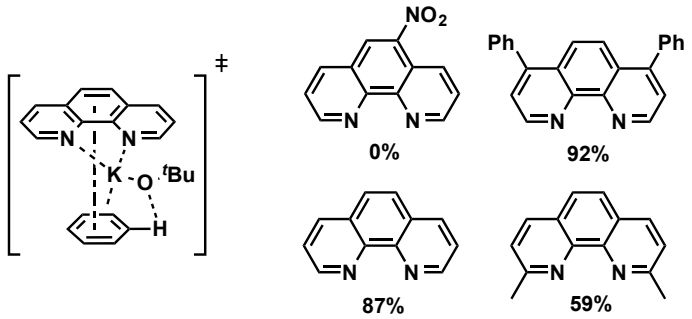
Figure 3

2.3.1. The Role of Phenanthroline Derivatives

Phenanthroline derivatives have been used for many decades in coordination chemistry, since an account of their use as colourimetric indicators by Chapman *et al.* in 1931.[67] Such ligands are common in transition metal chemistry, with 1,10-phenanthroline acting as a bidentate ligand and forming strong complexes with most metal ions.

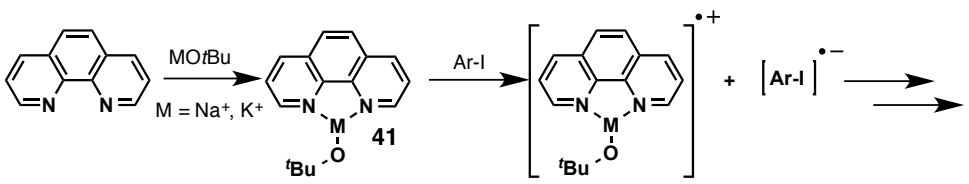
In transition metal-free cross-coupling reactions, however, Shi and coworkers have proposed an alternative role for 1,10-phenanthroline.[54] The potassium cation and 1,10-

phenanthroline interact with benzene *via* ion-π and π-π stacking interactions respectively. Such an interaction would seem feasible given experimental results that showed a decreased efficiency for more electron-deficient or sterically hindered phenanthroline derivatives (**Scheme 36**). The authors draw parallels with the proposed role for *N*-containing heterocycles in the work of Itami *et al*.[53] However, the authors present no further support for the intermediate, and fail to take into account the observed radical nature of the reaction.



Scheme 36

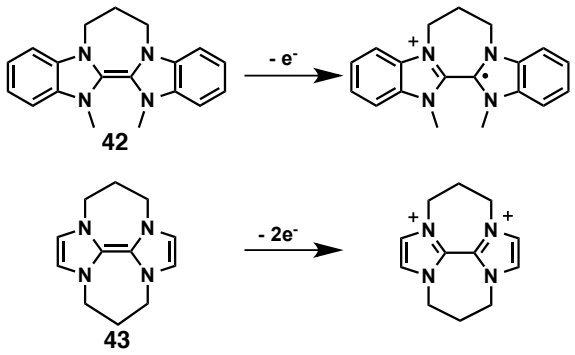
Using the well established ability of phenanthrolines to behave as bidentate ligands as a start point, Hayashi *et al.* proposed an initial complex formation between potassium or sodium *tert*-butoxide (**41**), and subsequent single electron transfer from this complex to initiate the coupling reaction (**Scheme 37**)[55]. Shi *et al*. also amend their original ion-π and π-π stacking intermediate to propose the formation of the same complex from KO^{t}Bu in a subsequent publication concerning the arylation of alkenes.[68]



Scheme 37

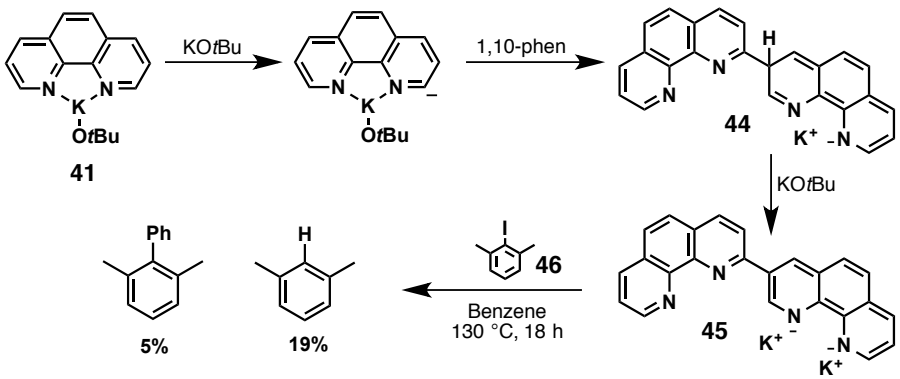
Murphy *et al.* have employed computational calculations to determine that the free energy change for the transformation of **Scheme 37** is inherently unfavourable. In light of these calculated free energy changes, Murphy and coworkers have proposed an

alternative role for the 1,10-phenanthroline additives in the radical initiation step.[69] Previous research from the group had shown that molecules such as **42** and **43** can act as "super electron donors", and behave as excellent electron transfer agents, capable of forming aryl radicals[70] or aryl anions[71] respectively from aryl iodides (**Scheme 38**).



Scheme 38

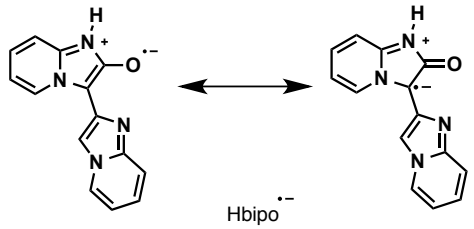
The reducing ability of these super electron donors arises from the aromatic stabilisation achieved upon loss of an electron(s). In light of this, Murphy applied a similar analysis to 1,10-phenanthroline in an attempt to understand the mode of operation (**Scheme 39**). An initially formed complex **41** can be deprotonated by KO^{t}Bu, followed by nucleophilic addition at the 3-position of 1,10-phenanthroline to give **44**. Further deprotonation by KO^{t}Bu yields **45**, which bears a strong resemblance to **42** and **43**, containing very electron rich heterocycles that can regain aromaticity by the loss of two electrons. The use of 2,6-dimethyliodobenzene **46** precludes benzyne formation and thus strongly suggests that an aryl radical is formed. The low yield of biaryl is presumably a result of steric hindrance.



Scheme 39

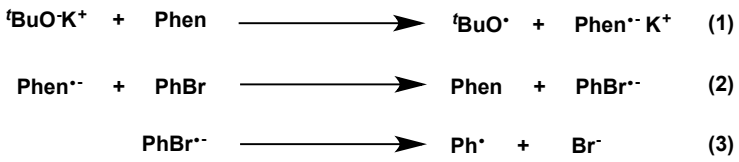
The authors also suggest that the formation of a generic super electron donor structure (*c.f.* **Scheme 38**) may account for the positive results observed when *N*-heterocyclic carbenes are used as additives in place of phenanthroline derivatives.[62]

Similar species have also been employed in arylation reactions by Yong *et al.*,[63] who found that a stable, zwitterionic radical containing a biimidazole core (Hbipo$^{\bullet-}$) was crucial to the success of the reaction (**Scheme 40**).



Scheme 40

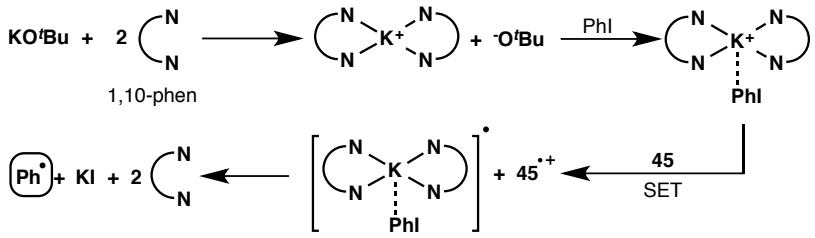
Recently, Lei *et al.*[72] have proposed an alternative role for phenanthroline ligands in the initiation of the coupling of bromobenzene and benzene. Using a combination of EPR and electrochemistry, the authors showed that 1,10-phenanthroline acts as a redox catalyst, reducing bromobenzene to an aryl radical, *via* the radical anion of phenanthroline (**Scheme 41, step 2**). The phenanthroline radical anion is itself formed *via* an initial electron transfer from KO^{t}Bu to phenanthroline (**Scheme 41, step 1**). The aryl radical generated in step 3 can then react with benzene, and eventually form the observed biaryl.



Scheme 41

In attempting to clear the confusion regarding the origin of phenyl radicals, Patil has very recently used computational means to consider the origin of the electron transfer to aryl iodides in the presence of phenanthroline derivatives.[73] Taking a lead from the super electron donors of Murphy *et al.*,[69] Patil suggests that an initially formed complex of 1,10-phenanthroline and potassium cation is expected to be a strong

electron acceptor, and forms a further complex with iodobenzene. Single electron transfer from super electron donor **45** generates a radical intermediate, which subsequently dissociates to form phenyl radical, potassium iodide and 1,10-phenanthroline (**Scheme 42**).



Scheme 42

Subsequent addition of the phenyl radical to benzene yields the biaryl as previously described. However, the author makes no comment on widely observed phenomena, such as the superiority of potassium *tert*-butoxide compared to sodium and lithium analogues in the synthesis of biaryls.

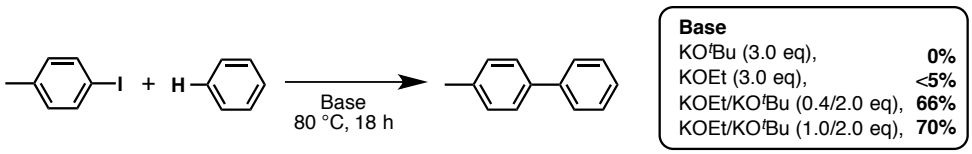
2.3.2. The Role of Diamines and Diols

Whilst several plausible mechanisms have been proposed for the role played by phenanthroline derivatives in the generation of aryl radicals, far less work has concerned the role of diamine or diol additives in the same initiation step. Indeed, few modes of action beyond acting as coordinating ligands for the strong base have been advanced.

2.3.2.1. Alcohols

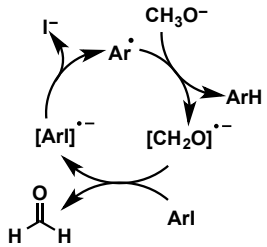
Liu *et al*.[61] disclosed a coupling procedure that utilised simple primary or secondary alcohols added at a 40 mol% amount. The authors suggest the origin of the reactivity to be the *in situ* formation of primary or secondary alkoxides from alcohols. To lend further weight to this hypothesis, mixed potassium alkoxide systems were employed (**Scheme 43**). Whilst KO^{t}Bu alone could not promote the reaction, and KOEt gave the biaryl in only 3% yield, a 1:2 mixture of KOEt:KO^{t}Bu efficiently promoted the reaction, giving the biaryl in a 70% yield. Although undoubtedly successful in promoting the reaction, an increase in activity *via* an increase in the amount of primary alkoxide would seem counter intuitive, given the greater reducing power of the tertiary

base KO^{t}Bu compared to KOEt. The combination of primary and tertiary alkoxide may facilitate single electron transfer at milder temperatures, whereas potassium *tert*-butoxide is required to deprotonate the intermediate cyclohexadienyl radical, hence the lack of reaction in the presence of either KOEt or KO^{t}Bu alone.



Scheme 43

In studying dehalogenation reactions undergone by aryl iodides in the presence of methoxide ions, Bunnett[74] has also highlighted the possibility that alcohol additives form alkoxides *in situ*. However, the author points out that this step may be followed by hydrogen abstraction to yield a carbonyl radical anion intermediate (**Scheme 44**). Electron transfer from the carbonyl radical anion to an aryl iodide would generate a carbonyl species, as well as an aryl iodide radical anion, which would allow for the generation of an aryl radical upon cleavage of the carbon-iodine bond, as previously described.

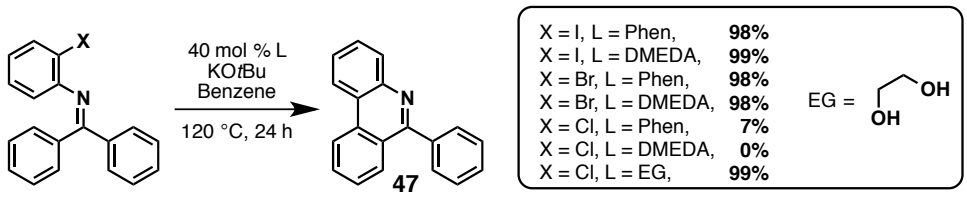


Scheme 44

Such a mechanism would account for observations made by Liu *et al*.,[61] such as the failure of the reaction with tertiary alcohols.

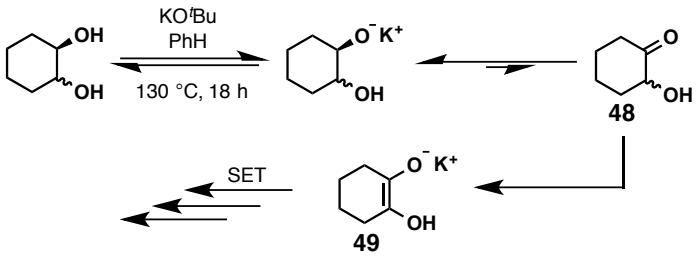
In their synthesis of phenanthridines **47** *via* an *intra*molecular arylation, Kwong *et al*. made use of the addition of 10 mol% of ethylene glycol (EG) as catalyst.[75] This inexpensive reagent was one of a number that could initiate the reaction of bromo- and iodo-starting materials (1,10-phen and DMEDA were also successfully used), though significantly was alone in promoting the reaction of chlorides (**Scheme 45**). With

greater chain lengths leading to a diminished efficiency, the authors conclude that a 1,2-diol is required to maximise coordination of potassium. A single electron transfer from the coordinated species to the aryl halide subsequently initiates the reaction.



Scheme 45

Murphy *et al.*[76] have again tried to rationalise the mode of action of alcohols in terms of the *in situ* formation of electron donors, characterised by electron rich alkenes. In their analysis of cyclohexane-1,2-diols, the authors propose that the alkoxide formed upon treatment with KO^{t}Bu can undergo base promoted oxidation to 2-hydroxycyclohexanone **48** according to the Woodward modification of Oppenauer oxidation (**Scheme 46**).[77] Whilst benzophenone is generally used as an oxidant in such oxidations, in this case the nature of the oxidant is unclear. Deprotonation to give **49** yields an extremely electron rich enolate, which is proposed to behave as a single electron transfer agent.



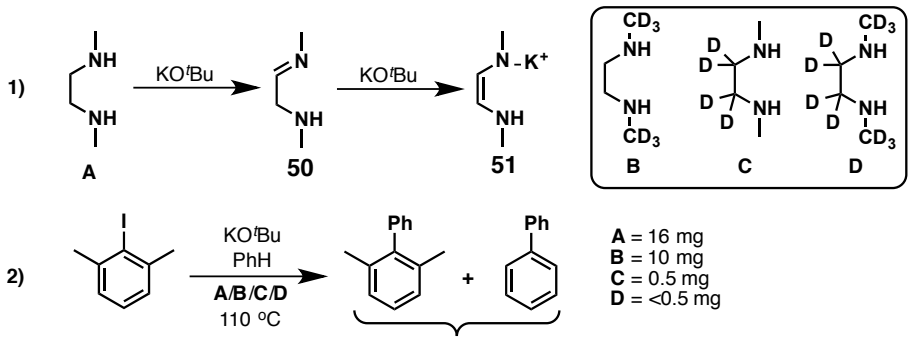
Scheme 46

However, the model does not take into account differences in the yield of biaryl product when *cis*- or *trans*-cyclohexane-1,2-diols are used. Combined yields of biaryl and reduced product of 32% and 64% for the *cis*- and *trans*- isomers respectively were obtained, despite the reaction proceeding *via* the same enolate intermediate. This discrepancy is even starker in the work of Kwong and Lei,[56] in which the yields of biaryl obtained from the coupling of 4-iodotoluene and benzene are 81% and 22%

when using *cis*- and *trans*-cyclohexane-1,2-diol respectively. In addition, the hypothesis could be tested by deprotonating an independently synthesised sample of **48**.

2.3.2.2. Diamines

The role of diamines in the promotion of biaryl coupling reactions has received much less attention than phenanthroline derivatives. In their initial discovery of the utility of DMEDA, Kwong and Lei *et al*.[56] make no reference as to the role played by DMEDA in the initiation of a radical chain process. Later, Kwong[75] also neglects to speculate as to the role played by DMEDA during the arylation of aryl iodides and bromides in the synthesis of phenanthridines (**Scheme 45**). In attempting to rationalise the role of DMEDA (and other 1,2-diamines) in the initiation step of biaryl formation, Murphy *et al*.[76] have again invoked the *in situ* formation of electron-rich double bonds as a precursor to electron transfer. Drawing on the work of Wotiz *et al*.[78] which showed that pyrazine radical anions form *via* loss of hydride upon treatment of ethylenediamine with strong base, deprotonation of DMEDA could give rise to an imine **50** (**Scheme 47**). A second deprotonation step would afford an electron rich alkene **51**, structurally very similar to previously postulated super electron donors. Reaction using 2,5-dimethyliodobenzene **46** could then proceed, again eliminating a benzyne mechanism, and producing the expected biaryl and reduced products. In order to determine if loss of hydride from **A** is the rate-determining step in the synthesis of **51**, changing a C–H bond to C–D would be expected to slow the formation of **51**, and hence reduce the efficiency of formation of the radical anion of **46**. Upon conducting parallel reactions under conditions that ensured incomplete conversion of **46**, the use of deuterated analogues of DMEDA (**B**-**D**) suggested that a kinetic isotope effect was in operation. The significantly smaller amount of coupled products obtained when using **C** and **D** suggest that cleavage of a C-H/C-D bond could be the rate-determining step in electron donor synthesis. However, only combined masses of product were divulged, and not yields of the individual products, making direct comparison difficult. In addition, under the proposed mechanism, the formation of imine **50** should not be affected when using diamine **A** or **B**. Therefore, there should be no difference in the observed product formation, which is clearly not the case.

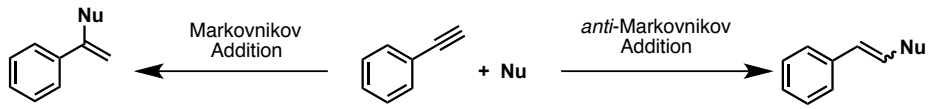


Scheme 47

The synthesis of biaryls in the absence of a transition metal is extremely significant for both economic and ease of handling reasons, and justifies the large amount of research conducted in the area. Whilst chemists have proved adept at identifying additives that facilitate the reaction, and several plausible mechanisms have been suggested to account for the formation of products, there remains a considerable lack of understanding as to the role played by additives in the generation of an intermediate radical species. Many of the mechanisms that have been suggested are unable to account for widely observed phenomena, such as the differences in reactivity of the various metal alkoxides employed. As such, attempts to improve the understanding of the initiation mechanism would represent an extremely important contribution to the area.

3. Terminal Alkynes and Enol Ether Synthesis

The development and mechanistic understanding of procedures that create carbon-oxygen bonds are of significant synthetic interest. The addition of an oxygen nucleophile to an unsaturated unit (alkene or alkyne) is one of the simplest approaches to C-O bond construction, and allows ready access to synthetically useful molecules such as enol ethers. In any addition to an unsaturated unit, issues of regioselectivity must be considered, with addition occurring in either a Markovnikov or *anti*-Markovnikov fashion (**Scheme 48**). With alkenes as products, *E*- and *Z*-selectivity must also be borne in mind.



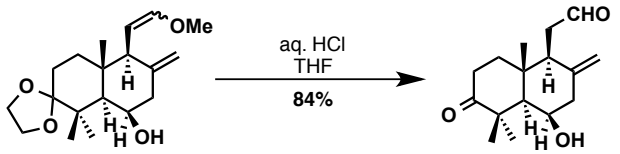
Scheme 48

3.1. Synthetic Uses of Enol Ethers

The addition of an oxygen-centred nucleophile to an alkyne is one of the most important routes to access enol ethers. Since the first synthesis of ethyl vinyl ether by Wislicenus in 1878,[79] enol ethers have represented a desirable and versatile building block in organic synthesis, with reactivity intermediate between that of an alkene and an enamine.[80] Synthetically useful applications have included, but are by no means limited to, the conversion to carbonyl containing compounds, use as cross-coupling substrates, ring closing metathesis and cycloaddition reaction substrates. There follows a brief overview of selected, representative reactions undergone by enol ethers.

3.1.1. Hydrolysis to Carbonyls

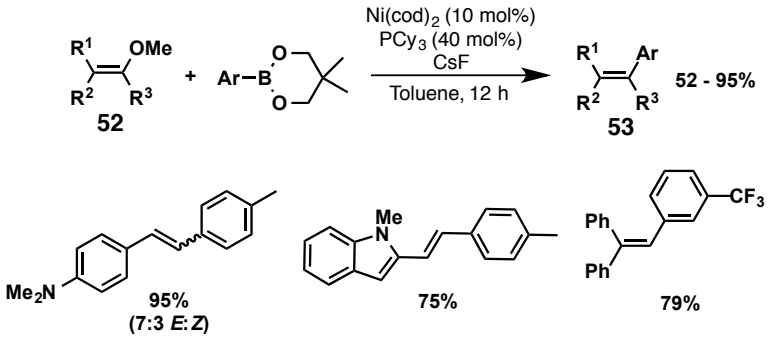
Most significantly, acidic hydrolysis of enol ethers affords ketone or aldehyde derivatives. An excellent example of the utility of enol ethers as masked carbonyls is provided by Jung *et al.*[81] in the synthesis of (±)-Kellermanoldione. The key transformation came as the penultimate step of a lengthy synthesis, demonstrating the functional selectivity afforded by the methyl enol ether (**Scheme 49**).



Scheme 49

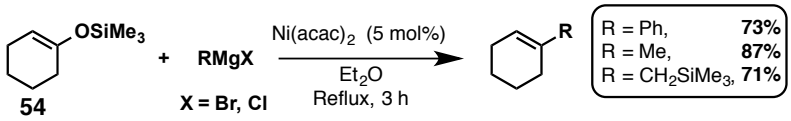
3.1.2. Cross-Coupling Substrates

Enol ethers have also found roles as substrates for cross-coupling reactions. Chatani *et al*.[82] have demonstrated the use of alkenyl methyl ethers **52** in a nickel-catalysed Suzuki-Miyaura coupling. Previously mainly limited to the use of organohalides and sulfonic esters, the use of enol ethers represents a significant improvement in terms of reaction scope, allowing access to a wide range of stilbene derivatives **53** in good yields (**Scheme 50**).



Scheme 50

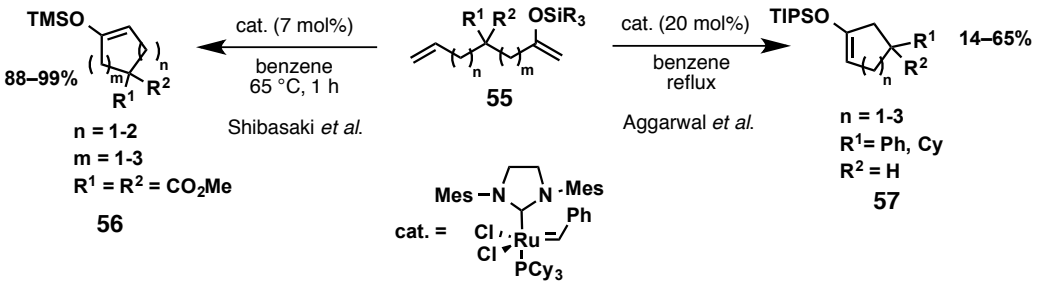
Kumada *et al*.[83] have also demonstrated the utility of enol ethers as cross-coupling substrates, forming olefins in high yield *via* a nickel catalysed reaction with Grignard reagents (**Scheme 51**). Whilst alkenyl halides would be the general reagent for the eponymous Kumada coupling reaction, limitations encountered in the synthesis of stereodefined alkenyl halides can be circumvented by the use of silyl enol ethers **54**, the synthesis of which can be conducted stereo- and regioselectively.



Scheme 51

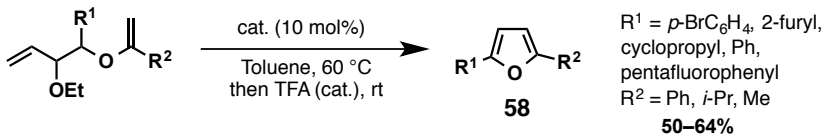
3.1.3. Ring Closing Metathesis (RCM)

Silyl enol ethers have again proven useful in synthesis, this time as substrates for ring closing metathesis reactions. Shibasaki *et al*.[84] and Aggarwal *et al*.[85] both utilised Grubbs' second generation catalyst in the RCM of silyl enol ethers **55**, generating cyclic enol ethers (**56** and **57**) in excellent and moderate yields respectively (**Scheme 52**). Such reactions constitute the first highly regioselective syntheses of cyclic silyl enol ethers.



Scheme 52

Aggarwal attempted to extended the reaction conditions to methyl enol ethers, though with only moderate success. Further modification of substrates by Donohoe *et al*.[86] has opened access to 2,3-dihydrofurans, which may be further oxidised *in situ* to yield 2,5-disubstituted furans **58** rapidly, and under mild conditions (**Scheme 53**). Again, Grubbs' second generation catalyst is used throughout.



Scheme 53

3.2. Synthesis of Enol Ethers

Despite the clear synthetic utility of enol ethers, application in synthesis *via* addition of a nucleophile to an alkyne has often been hampered by extremely harsh reaction conditions, or the use of toxic reagents. The following section will present selected examples of the addition of oxygen nucleophiles to alkynes, and does not consider the synthesis of enol ethers *via* alternative routes.

3.2.1. Historical Approaches

The addition of heteroatomic nucleophiles to an alkyne is a thermodynamically favourable process, though hampered by a high activation energy barrier.[87] In light of this, the addition of oxygen nucleophiles to alkynes has typically been achieved using unattractive reaction conditions such as strong acids, or toxic mercury reagents. In 1875, Schrohe and Fittig[88] demonstrated the hydration of propyne to give acetone upon exposure to concentrated sulfuric acid, presumably proceeding *via* an initial Markovnikov addition. Later, Kutscheroff[89] achieved the same conversion under milder conditions in the presence of dilute sulfuric acid and mercury(II) salts. The use of mercury(II) salts hence became the established method for the addition of oxygen nucleophiles to alkynes, with Hennion *et al*.[90] demonstrating the use of catalytic amounts of mercury(II) sulfate in the hydration of alkylacetylenes to yield ketones. The same workers extended the methodology beyond formation of ketones to give rise to acetals[91] and ketals[92], with mercuric oxide and boron trifluoride mediating the addition of methanol to acetylene and alkyl substituted terminal alkynes respectively. In all above cases, alkyl substituted terminal alkynes were used, and only the product arising from Markovnikov addition was reported.

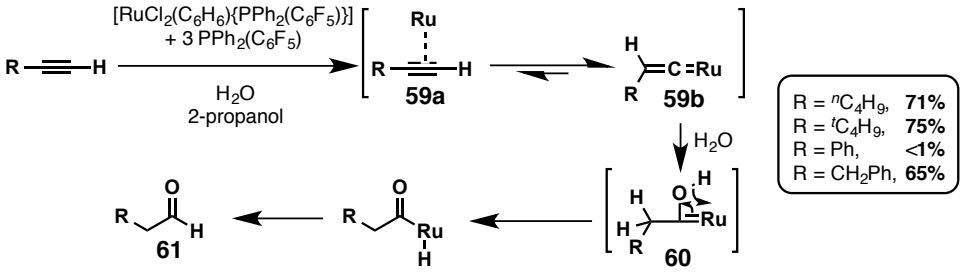
3.2.2. Transition Metal Catalysed Addition

Improving considerably upon the traditional approaches towards oxygen addition to alkynes, both in terms of selectivity and relative mildness of reaction conditions, the use of transition metals has allowed access to either Markovnikov or *anti*-Markovnikov products, often with excellent control of stereochemistry. However, the cost and inherent toxicity of some transition metals must always be borne in mind.

3.2.2.1. Hydration of Terminal Alkynes

With regards to the hydration of terminal alkynes, the use of various transition metal catalysts including Au(III),[93,94] Au(I),[95] Ru(III)[96] and $RhCl_3$[97] have mirrored the achievements made using mercury(II) salts, though yields are invariably significantly improved. Ketones are formed exclusively, arising from a Markovnikov addition pathway.

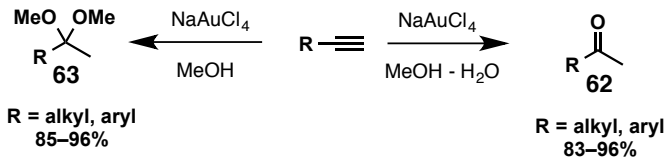
The first example of an *anti*-Markovnikov hydration of a terminal alkyne was presented by Wakatsuki *et al.*,[98] and relied upon the use of a ruthenium(II)/phosphane mixture to generate aldehydes. Ketones arising from Markovnikov addition were formed only in small yields. A proposed mechanism invokes an initial activation of an alkyne by the ruthenium(II) catalyst to give **59a**, which is in equilibrium with a vinylidene complex **59b**. The authors suggest that the addition of phosphane to the reaction acts to favour the formation of **59b**. Addition of water to the vinylidene carbon to form hydroxycarbene intermediate **60** is followed by a rearrangement, and reductive elimination to yield aldehyde **61** (**Scheme 54**)



Scheme 54

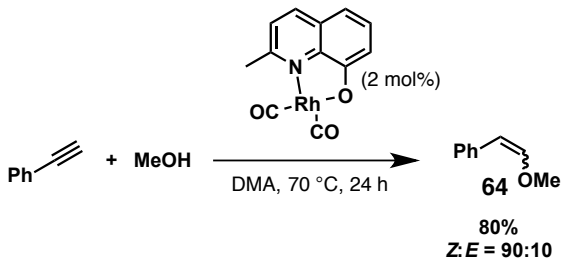
3.2.2.2. Addition of Alcohols to Terminal Alkynes

Gold catalysts have again found application in the addition of methanol to terminal alkynes. Similar to the reactions of terminal alkynes under mercury mediation, the addition is Markovnikov. Depending on reaction conditions, ketones or dimethylacetals may be synthesised (**Scheme 55**). Treatment of terminal alkynes with 2 mol% of sodium tetrachloroaurate in refluxing aqueous methanol gave rise to ketones **62** in excellent yields, whereas conducting the reaction in anhydrous methanol gave the corresponding dimethyl acetals **63**, again in excellent yields. Further Au(III) complexes have been used with similar success.[99]



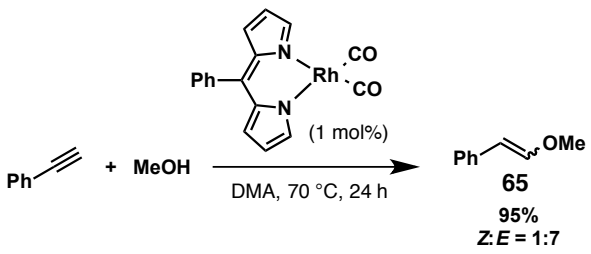
Scheme 55

Significant progress towards controlling the stereochemistry of addition was made when Kakiuchi *et al*.[100] reported the *Z*-selective, *anti*-Markovnikov hydroalkoxylation of arylacetylenes mediated by a rhodium catalyst (**Scheme 56**). Using simple alcohols as the nucleophiles, the method avoids the requirement for strongly basic reaction conditions. Though only applicable to terminal alkynes, reactions are tolerant of both electron withdrawing and donating groups, giving the *β*-alkoxystyrenes **64** in generally good yields. Although the mechanism of addition remains unclear, the authors propose the initial formation of a vinylidene-rhodium species. A computational analysis conducted by Wang *et al*. has provided further support for a vinylidene intermediate.[101] However, despite the superiority of the chosen catalyst compared to others that were screened, there is no indication that a control experiment to confirm the crucial nature of the rhodium catalyst was conducted.



Scheme 56

A similar vinylidene-rhodium intermediate has recently been invoked by Messerle *et al*.[102] to account for hydroalkoxylation of terminal alkynes. Similarly to Kakiuchi, only *anti*-Markovnikov products **65** are formed, though interestingly, under very similar reaction conditions to Kakiuchi, the *E*-isomer is instead favoured (**Scheme 57**). A mechanistic rationale is again not forthcoming, though the procedure, in combination with that of Kakiuchi, succinctly demonstrates the ability of transition metal catalysis to direct selectivity in enol ether synthesis. The downside of the reaction is the time taken to prepare the catalyst, which is formed in four steps in a low overall yield.



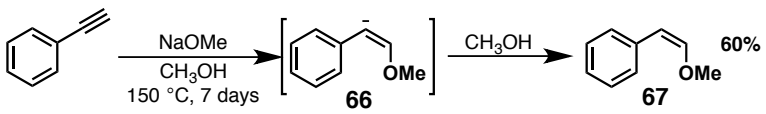
Scheme 57

3.2.3. Transition Metal-Free Synthesis - Addition of Alkoxides

In common with the synthesis of biaryls, transition metal-free syntheses of enol ethers are desirable due to cost, toxicity and purification considerations. Several transition metal-free, regioselective syntheses of arylacetylene-derived enol ethers have been published, but there lacks an understanding of the underlying mechanism.

The addition of alcohols to acetylenes in the absence of transition metal catalysts has been known for many years, and generally relies upon the use of strong bases to form alkoxides *in situ*. Whilst the addition of alkoxides to terminal alkynes has been used in isolated examples of synthesis for the generation of enol ethers,[103] a satisfactory explanation for the product distribution has remained elusive. Several trends have been consistently noted upon addition of alkoxides to aryl substituted terminal alkynes. Firstly, addition is *anti*-Markovnikov, either selectively or solely. Secondly, additions tend to favour the *Z*-enol ether.

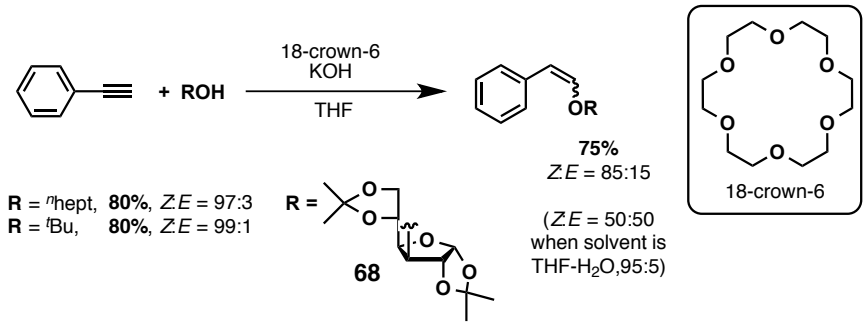
For instance, in contrast to the acetylene hydration reactions discussed previously, on treating phenylacetylene with sodium methoxide in methanol, Miller[104] noted a general trend of *trans*-addition of the alcohol to yield *anti*-Markovnikov addition products (though stereochemistry was assigned solely *via* analysis of IR stretching frequencies). This is in accordance with the findings of Truce *et al*. concerning the addition of thiols to aromatic alkynes.[105] A stepwise ionic mechanism is supposed, with an initial rate determining formation of a vinyl anion **66**, followed by rapid anion quenching to yield **67** (**Scheme 58**). However, the extremely long reaction time of seven days makes the procedure particularly unappealing.



Scheme 58

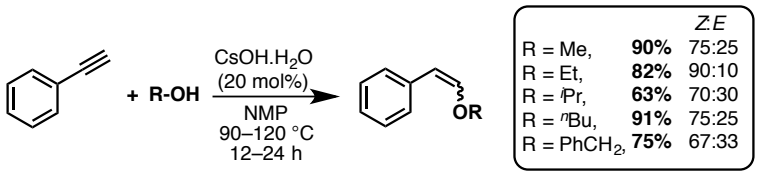
The same selectivity trends have also been observed in the work of Chiappe *et al*.[106] Potassium hydroxide and a catalytic amount of 18-crown-6, a molecule that exhibits highly selective binding of potassium, promote the addition of primary, secondary or tertiary alcohols to phenylacetylene with almost exclusive *anti*-Markovnikov addition

(**Scheme 59**). The addition also shows high *Z*-selectivity, and tolerates several sterically congested carbohydrate derivatives such as **68**. Again, a stepwise mechanism proceeding *via* an intermediate carbanion is proposed. Interestingly, the authors noted that *Z*-selectivity is totally diminished when the reaction is run in non-anhydrous THF.



Scheme 59

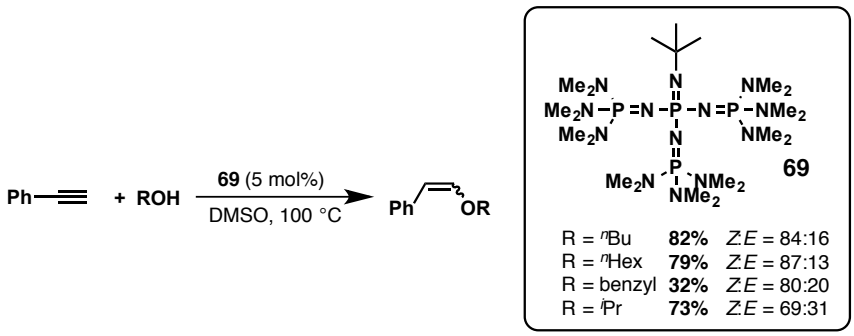
Knochel *et al*.[107] have shown that, upon stirring alcohols and phenylacetylene with a substoichiometric amount of cesium hydroxide in NMP for 12 hours at 100 °C, *anti*-Markovnikov addition products are again formed with high *Z*-selectivity (**Scheme 60**). Although only phenylacetylene was studied, and alcohols were limited to 1° and 2° examples, yields were generally good, and *Z*:*E* ratios remain approximately constant at ~ 7:1, regardless of the alcohol chosen. The isolation of both *Z*- and *E*-isomers is attributed to the high reaction temperature, with no further mechanistic insight presented.



Scheme 60

A substoichiometric additive has also been employed by Kondo *et al*.[108] in the functionalisation of phenylacetylene. The phosphazene base **69** was used at 5 mol% in DMSO, generating exclusively *anti*-Markovnikov addition products, in good yields and with high *Z*-selectivities. Again extremely limited in scope, only 1° and 2° alcohols were investigated, and *Z*:*E* values remained similar for each primary alcohol

used (**Scheme 61**). Similarly to reactions conducted in the presence of alkali metal systems, the reaction proceeds *via* the initial formation of an alkoxide.



Scheme 61

Enol ether synthesis *via* the addition of a nucleophile to a terminal alkyne is a commonly used reaction in chemistry, and is often assumed to proceed simply *via* a nucleophilic addition reaction. However, whilst giving rise to synthetically useful substrates, there has been little work devoted to determining the underlying mechanism of addition. Successful examples presented in the literature are often strongly dependent upon the identity of the alkyne, generally requiring aromatic substitution. Such aromatic alkynes present a readily reducible substrate, which could behave as an efficient electron acceptor. Therefore, the possibility that alternative reaction mechanisms are in competition, or indeed predominate, must be borne in mind.

4. Alkynyl Sulfides

Alkynyl sulfides are important synthetic intermediates, finding uses in further chemical transformations such as cycloaddition reactions, metal catalysed cross-couplings, and as useful intermediates in the synthesis of natural products.[109] To date, the most common method for the synthesis of alkynyl sulfides exploits the reaction between a deprotonated terminal alkyne, and a sulfur-containing unit with an appropriate leaving group (**Figure 4**). Examples employing disulfides, thiosulfonates,[110] sulfenamides,[111,112] bromides,[113] and thiocyanates[114] exist in the literature, allowing access to a wide variety of alkynyl sulfides.

4.1. Synthesis of Alkynyl Sulfides

4.1.1. ^{n}BuLi Deprotonation of Terminal Alkynes

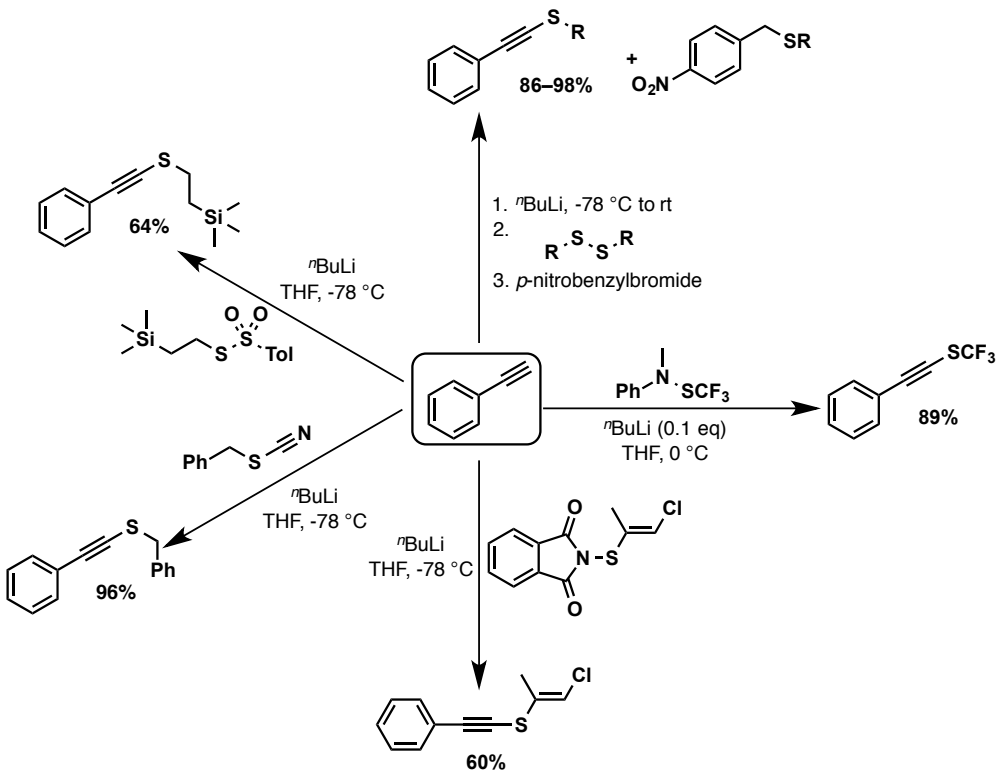
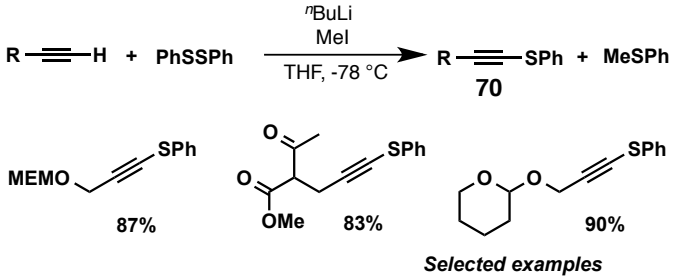


Figure 4

Despite the apparent variety in suitable reagents, many such reactions are severely limited in their scope, being used to prepare only a small number of alkynyl sulfides as novelties when required in the synthesis of further products.[115] In addition, such an

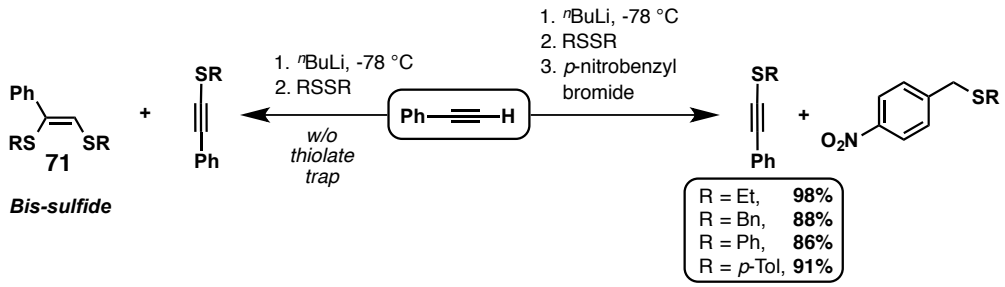
approach by definition necessitates a stoichiometric amount of base, limiting the scope of reactions to substrates that are stable under such conditions.

The ^{n}BuLi-mediated reaction of terminal alkynes with disulfides has been known for many years. Kabanyane and MaGee[116] reported one of the first general, high yielding methods utilising terminal alkynes and diphenyldisulfide, allowing the synthesis of a range of thiophenol-substituted alkynes **70** (**Scheme 62**).



Scheme 62

The range of compounds is strictly limited to alkyl-substituted alkynes, and there is no indication that further disulfides are applicable to the reaction. The conjugate thiolate anion formed renders such processes vulnerable to further addition to give a bis-sulfide by-product **71**. As such, thiolate traps such as methyl iodide[116] have often been included. Tam *et al*.[117] made use of *p*-nitrobenzylbromide as an efficient thiolate trap in extending the reaction scope (**Scheme 63**).

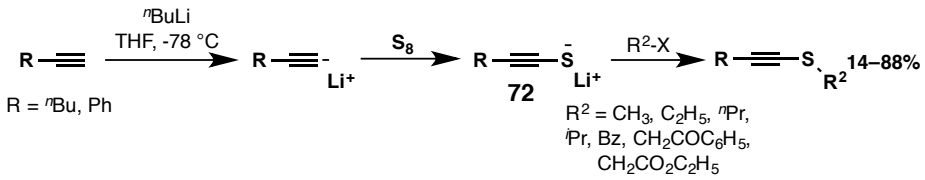


Scheme 63

In most cases, the sulfur-containing moieties of **Figure 4** must be formed from the parent thiol, adding an additional step to any synthesis. This also introduces the complication that starting materials often exceed the complexity of products, hence leading to particularly atom inefficient processes.

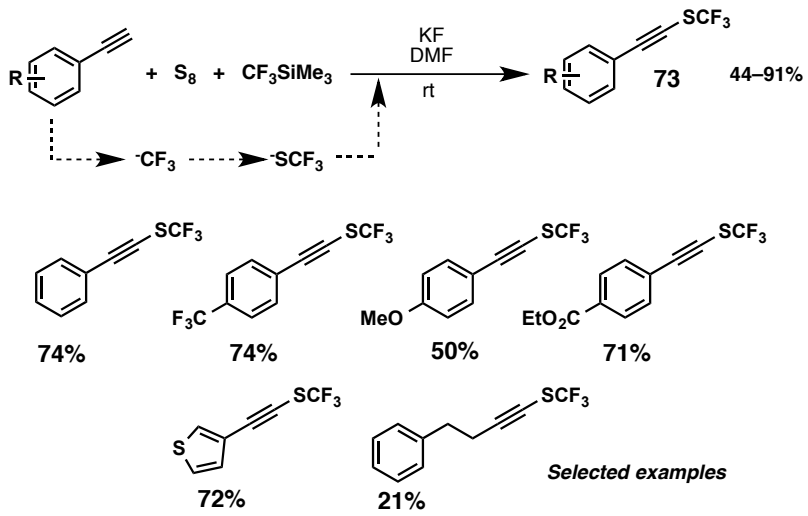
4.1.2. Use of Elemental Sulfur

A subtly different approach has made use of elemental sulfur in the synthesis of alkynyl sulfides. Hu *et al*.[118] have demonstrated that the treatment of a terminal alkyne with ^{n}BuLi followed by sulfur gives rise to alkynyl thiolate **72**, which can be quenched by the addition of a wide variety of alkyl halides (**Scheme 64**). The reaction is wide ranging, being applicable to both alkyl and aryl substituted terminal acetylenes. In addition, numerous alkyl bromides and iodides can act as efficient thiolate traps, yielding alkynyl sulfides rapidly and in good yields, and without the use of malodorous thiols.



Scheme 64

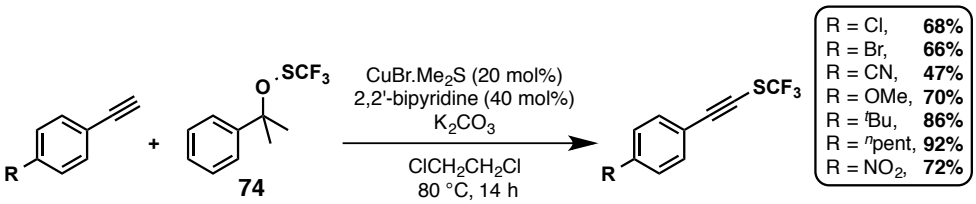
Elemental sulfur has also been used by Qing *et al*.[119] though a somewhat different role is proposed (**Scheme 65**). Instead of behaving simply as a precursor of an alkynyl thiolate anion, the authors propose elemental sulfur to act as an oxidising agent, assisting in the generation of an anionic SCF_3 species. Reaction of the anionic species with phenylacetylene yields alkynyl sulfides **73**.



Scheme 65

The SCF_3 substituted alkynes are generated in moderate to good yields, and constitute particularly interesting compounds owing to the strong electron-withdrawing capacity, and high lipophilicity of the SCF_3 group.[120] With ^{n}BuLi not required in the reaction, substrates containing halo substituents were also well tolerated. However, the reaction requires a large excess of the expensive Ruppert-Prakash reagent.

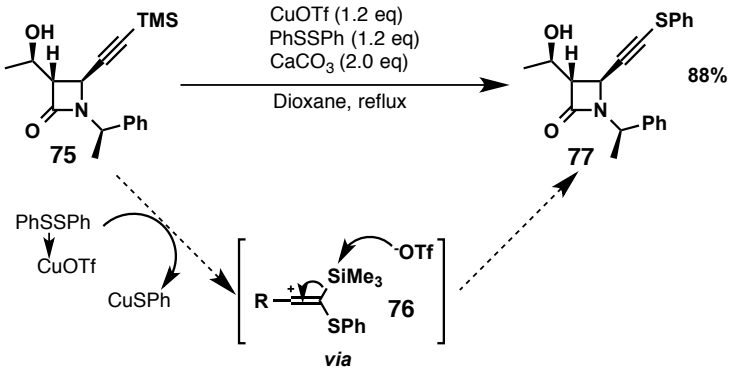
Recently, Shen *et al*.[121] have shown that the same trifluorothiolated products can be generated from terminal alkynes and trifluoromethanesulfenate **74**, under copper catalysis (**Scheme 66**). Though yields are generally comparable to those reported by Qing *et al*., the combination of a considerably higher reaction temperature, an excess of the terminal alkyne and use of metal catalyst, makes this approach less attractive than that of Qing. In addition, the trifluoromethylthiolating reagent must be prepared, adding further time to synthesis.



Scheme 66

4.1.3. Synthesis *via* Silyl Substituted Alkynes

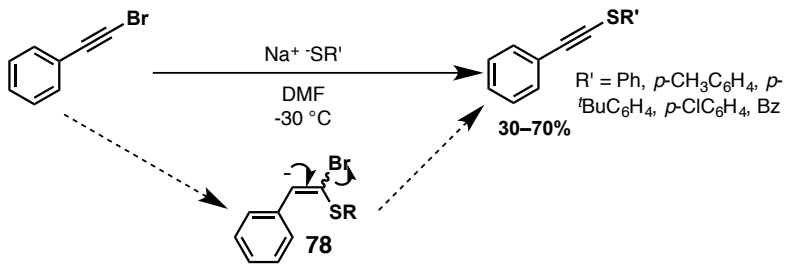
A copper catalyst has also been employed by Shibasaki *et al*.[109] in the synthesis of *Thienamycin* intermediates **77** *via* alkynyltrimethylsilanes **75** (**Scheme 67**). The complex formed upon combination of diphenyl disulfide and copper(I) triflate is proposed to act as a powerful source of PhS^+, generating the intermediate **76** upon reaction with an alkyne. Elimination of the silyl group by triflate anion would hence give rise to the alkynyl sulfide. Although limited to a single example, the procedure emphasises the importance of being able to introduce alkynyl sulfides into natural product synthesis.



Scheme 67

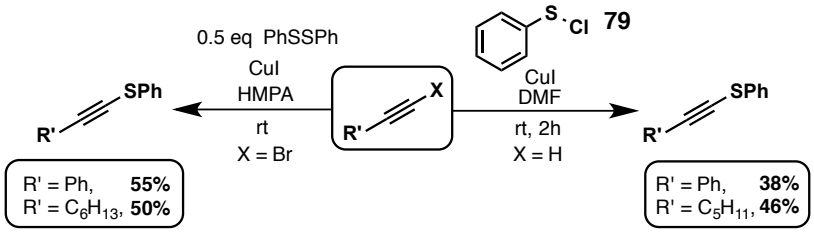
4.1.4. Bromoalkynes

1-Bromophenylacetylenes have proved to be useful substrates in the synthesis of alkynyl sulfides. Miller *et al.*[122] noted a previously unusual case of nucleophilic substitution at an *sp*-centre upon treatment of 1-bromophenylacetylene with sodium thiolates in DMF (**Scheme 68**). Limited to phenyl substituted acetylenes, alkynyl sulfides were prepared in acceptable to good yields following stirring for several hours. Described in terms of an ionic addition-elimination sequence *via* vinyl anion **78**, the reaction represents an interesting, single step displacement at an *sp*-centre.



Scheme 68

Bromophenylacetylenes have also been used by Braga *et al.*[123] in the copper(I) mediated synthesis of alkynyl sulfides. Again severely limited in scope (two examples), the reaction generates alkynyl sulfides in only moderate yields (**Scheme 69**, left). Although avoiding the need for a strongly basic environment, as is common in alkynyl sulfide synthesis, the use of potentially tricky alkynyl bromides and extremely toxic HMPA as solvent considerably limits the utility of the approach.

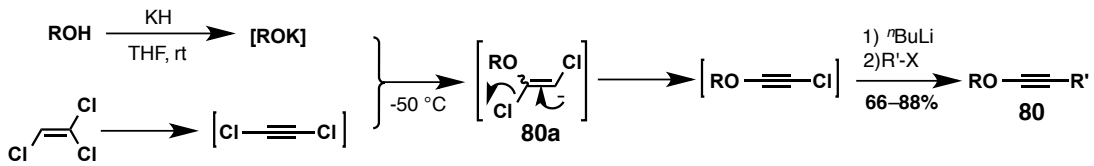


Scheme 69

The authors have, however, made some progress in rectifying some of these drawbacks *via* the development of an alternative alkynyl sulfide synthesis utilising terminal alkynes and chlorinated thiophenol **79** (**Scheme 69**, right).[124] However, the use of an excess of copper iodide, poor yields and a similarly limited scope has again precluded widespread adoption of the procedure.

4.1.5. Dibromoalkenes

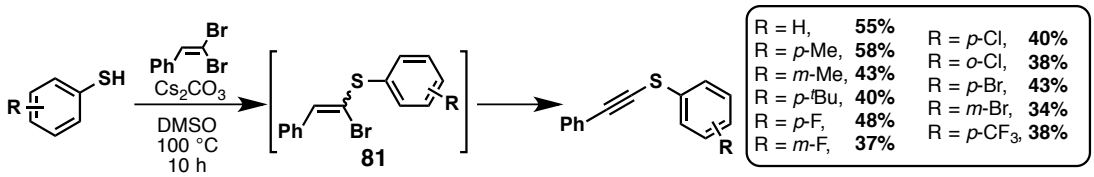
The structurally related ynol ethers **80** have historically been synthesised *via* the elimination of halogens from alkenes, particularly trichloroethylene, with Greene *et al*. disclosing the first general approach (**Scheme 70**).[125] A potassium alkoxide is formed *in situ*, and reacts with dichloroethyne to yield adduct **80a**. Upon lithiation and quenching with an alkyl halide, ynol ether **80** is formed in high yield.



Scheme 70

Extending this concept to alkynyl sulfides, Pan *et al*.[126] have recently disclosed a simple coupling between thiophenol derivatives and *gem*-dibromoalkenes. Initial formation of the monobrominated product **81** is followed by Cs_2CO_3 mediated elimination to cleanly yield the alkynyl sulfide (**Scheme 71**). Although yields are at best moderate, the transition metal-free reaction conditions can tolerate a wide scope of both thiophenols and readily prepared dibromoalkenes, with examples of both electron withdrawing and donating functionalities. However, the time and high temperature required to prepare the derivatives may be seen as something of a

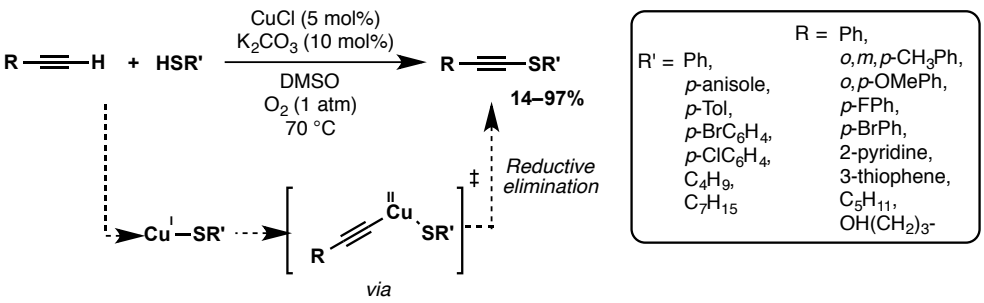
drawback. In addition, only thiophenol derivatives are tolerated in the reaction, with no indication of alkyl-thiols working successfully.



Scheme 71

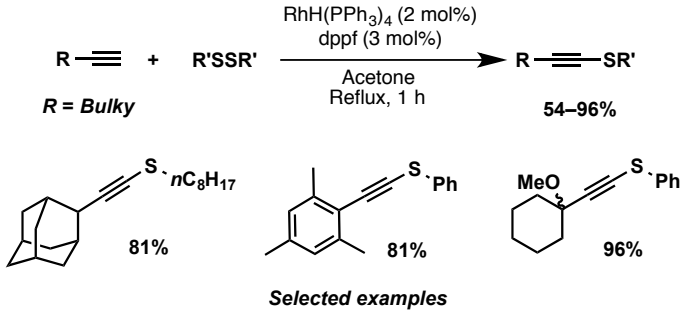
4.1.6. Further Metal Mediated Syntheses

Of the methods used for the synthesis of alkynyl sulfides, many suffer from the use of substrates that themselves are more complex and time intensive to synthesise than the desired product. Combatting this, Rioux and Yang *et al.*[127] have recently disclosed a mild coupling of terminal alkynes and free thiols under copper catalysis (**Scheme 72**). Using molecular oxygen as the oxidant, the procedure is applicable to a wide range of terminal alkynes (aromatic and aliphatic) and thiols (aryl and alkyl), generating the alkynyl sulfides in generally good yields.



Scheme 72

The scope of metal-catalysed reactions proceeding *via* a disulfide has been considerably extended in the work of Yamaguchi *et al.*,[128] in which a catalytic amount of a rhodium complex is used to promote reaction between a terminal alkyne and disulfide (**Scheme 73**). Compared to many other alkynyl sulfide syntheses, there is no requirement for a stoichiometric amount of base, with the rhodium complex instead playing a role in alkyne C-H activation, disulfide cleavage, and alkyne-sulfur bond formation.



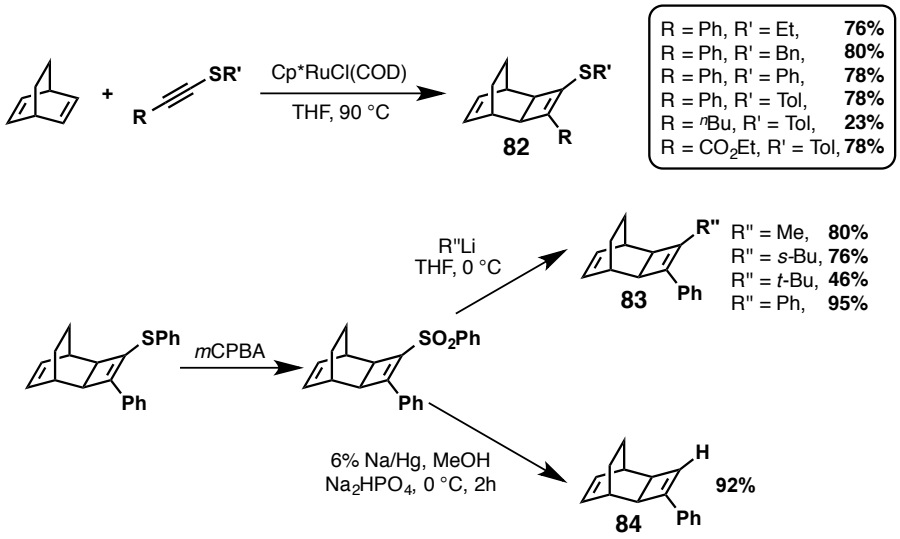
Scheme 73

Although applicable to a considerably wider array of alkynyl sulfides than many previously published routes, with examples of alkyl and aryl substituted analogues, the authors note the requirement for a bulky group on the terminal alkyne to prevent alkyne dimerisation. For instance, in the reaction between *o*-tolylacetylene and dioctyldisulfide, the dimerisation product was isolated in 50% yield, with the expected alkynyl sulfide in only 28%. Overall however, the route gives quick access to a broad array of alkynyl sulfides from readily available terminal alkynes and disulfides.

4.2. Reactions of Alkynyl Sulfides

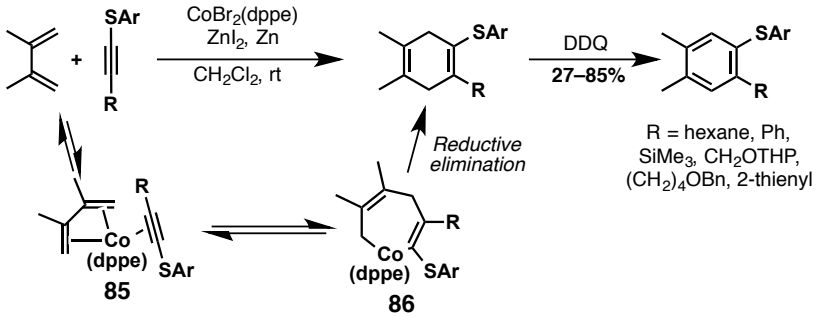
4.2.1. Substrates in Cycloaddition Reactions

Tam *et al*.[117] have demonstrated the ruthenium-catalysed cycloaddition between alkynyl sulfides and bicyclic alkenes (**Scheme 74**). Giving only the *exo*-product **82** in generally excellent yields, the procedure represents the first [2+2] cycloaddition of alkynyl sulfides. The use of a ruthenium catalyst in the presence of sulfur is not common due to coordination to the catalyst, and so a ruthenium catalysed reaction of alkynyl sulfides is significant. In addition, the cyclobutene adducts can be further derivatised *via* reaction with alkyl lithium reagents,[129] or undergo desulfonation using a 6% Na/Hg amalgam to yield products that are otherwise significantly more difficult to prepare (**83** and **84**).



Scheme 74

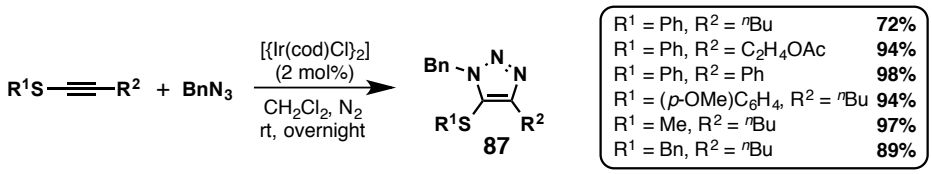
Hilt *et al*. also noted the problem of sulfur coordination to the transition metal catalyst in the cobalt catalysed Diels-Alder cyclisation of alkynyl sulfides.[130] As such, catalyst loadings as high as 50 mol% were required for the cyclisation to proceed with good yields. Nevertheless, the reaction conditions proved considerably milder and significantly more general than predecessors,[131] allowing access to a variety of cyclohexadienes, which may be subsequently oxidised by DDQ to the corresponding aromatic products (**Scheme 75**). The authors propose the mechanism to proceed *via* coordination of alkyne and diene to (**85**), then insertion of (**86**), the cobalt complex, followed by a reductive elimination to give the Diels-Alder products.



Scheme 75

Recently, Jia and Sun *et al*. have demonstrated an azide-alkyne cycloaddition reaction employing electron-rich alkynyl sulfides (**Scheme 76**).[132] Employing an iridium based catalyst, the reaction allows the synthesis of triazoles **87** in excellent yields and with

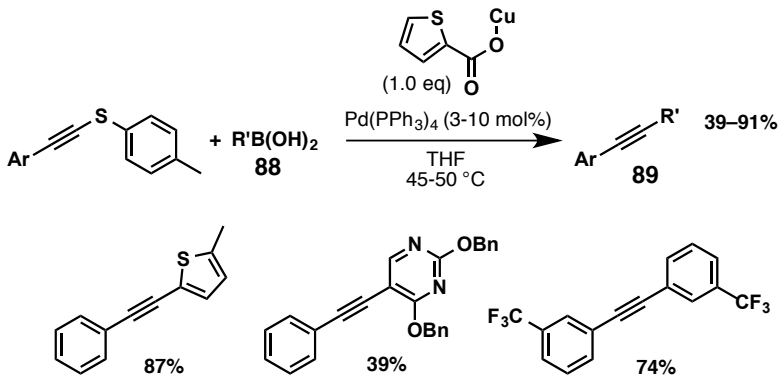
complete regioselectivity. In addition, the reaction conditions are tolerant of both moisture and air, allowing ready access to a range of triazoles under particularly mild conditions. Oxidation of the reaction products with *m*-chloroperbenzoic acid allows facile access to 5-sulfonyltriazoles, compounds that are difficult to synthesise in high yield and regioselectivity *via* the cycloaddition of analogous sulfonylacetylene compounds.



Scheme 76

4.2.2. Pd-Mediated Reactions of Alkynyl Sulfides

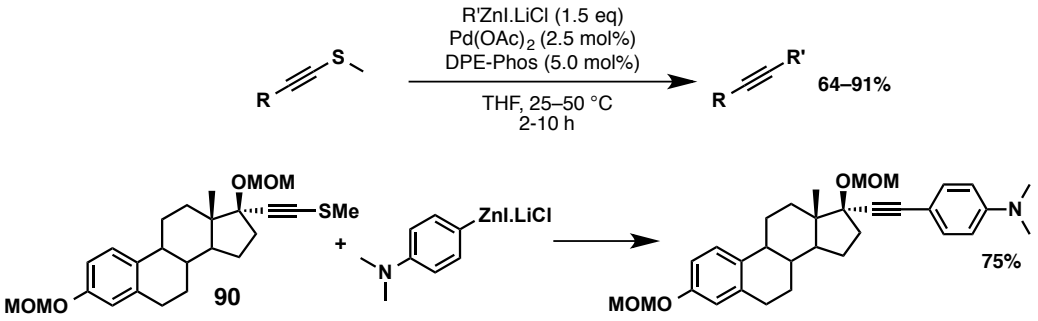
Liebskind *et al*.[133] have demonstrated the use of alkynyl sulfides in the Pd-catalysed synthesis of synthetically useful substituted alkynes. Employing boronic acids (**88**), alkynyl sulfides react under mild conditions to give disubstituted alkynes **89** in acceptable to excellent yields and with broad scope. This method provides an umpolung, complimentary approach to the Sonogashira reaction, and, unlike the Suzuki reaction, does not require basic conditions (**Scheme 77**).



Scheme 77

Knochel *et al*.[134,135] have used readily prepared organozinc reagents in the Pd-catalysed coupling of alkynyl sulfides. Again, yields are generally excellent, and the reaction is applicable to both aryl and alkyl substituted alkynyl sulfides. The reaction

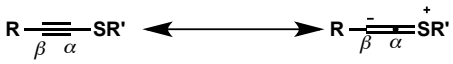
conditions are mild enough to tolerate ester functional groups, and the significance of the transformation to total synthesis has been nicely demonstrated by the functionalisation of an alkynyl sulfide substituted steroid **90** in good yield (**Scheme 78**).



Scheme 78

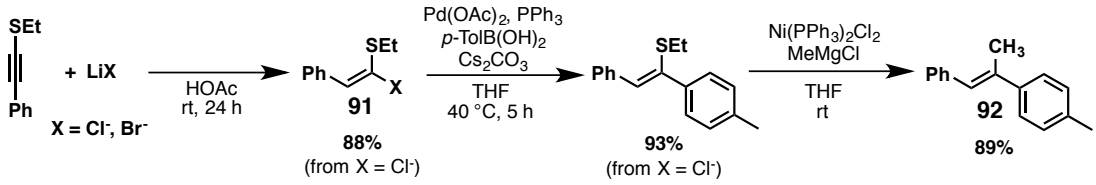
4.2.3. Access to Halo Vinyl Sulfides

The inherent polarisation of the alkynyl sulfide bond allows a greater degree of regiocontrol upon attack of the triple bond (**Scheme 79**), with preferential nucleophilic attack occurring at the relatively positively charged α-carbon.



Scheme 79

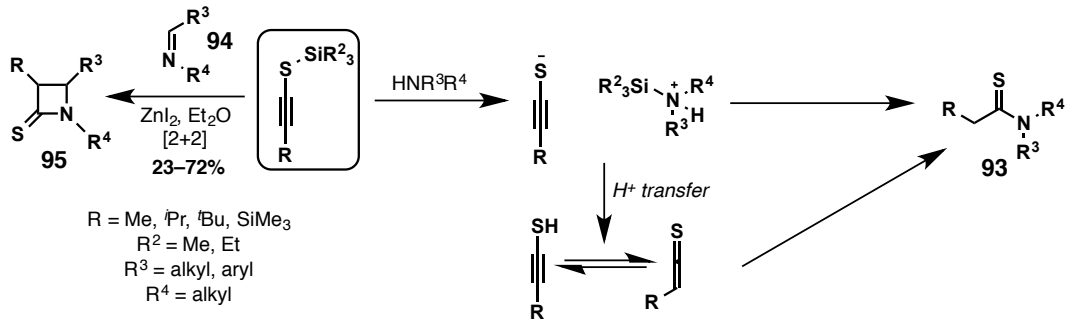
This degree of regiocontrol has been exploited by Zhu *et al.*[136] in the synthesis of synthetically useful, stereodefined α-halo vinyl sulfides from alkynyl sulfides. The initially mild *syn*-hydrohalogenation provides chloro- and bromo-vinyl sulfides **91** in excellent yields. Compared to the analogous reaction conducted on ynol ethers and reported by Jin *et al.*,[137] the halo vinyl sulfides are stable to purification *via* column chromatography prior to further product elaboration. The vinyl sulfides are well set up for differential functionalisation due to the differing reactivities of the carbon-halogen, and carbon-sulfur bonds, a considerable advantage compared to the use of 1,1-dihaloalkenes. Thus, the procedure allows ready access to regio- and stereodefined, trisubstituted alkenes **92** in high yields (**Scheme 80**).



Scheme 80

4.2.4. Alkynyl Silyl Sulfides as Thioketene Equivalents

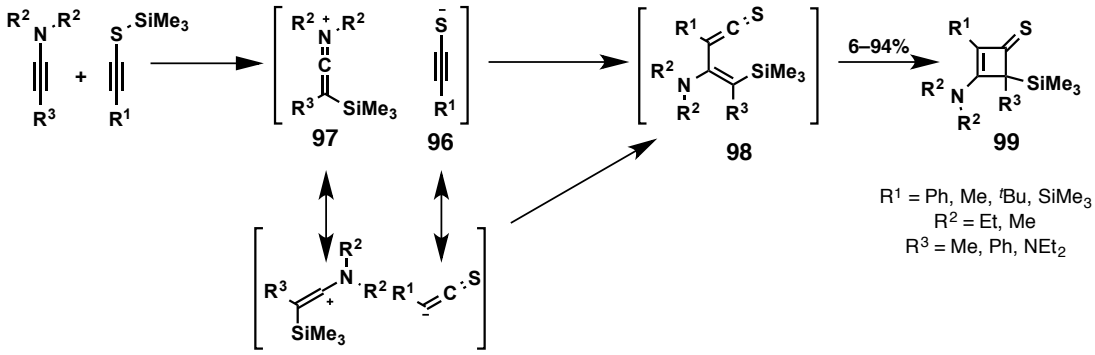
Schaumann and Spanka[138] have utilised alkynyl silyl sulfides as extremely versatile synthetic building blocks, exploiting their thioketene-like reactivity (**Scheme 81**). Alkynyl silyl sulfides are readily accessible from terminal alkynes. In particular, reactions with nitrogen nucleophiles have been well explored. The synthesis of thioamides **93**, which would otherwise be difficult due to the difficulties in accessing thioacyl chlorides or anhydrides, proceeds with alkynyl silyl sulfides and primary or secondary amines, though curiously the authors neglect to divulge yields and scope. In addition, reaction with azo-methines **94** enables access to a wide range of *β*-thiolactams **95**, the products expected *via* a [2+2] cycloaddition (**Scheme 81**). The inherent ring strain in such molecules would cause them to be difficult to prepare *via* the use of *β*-lactams and sulfur transfer reagents. However, the procedure is let down by very variable yields and diastereoselectivities.



Scheme 81

Alkynyl silyl sulfides have also been used by Schaumann *et al.* to provide access to 4-silylcyclobut-2-enethiones in variable yields *via* the reaction with ynamines (**Scheme 82**).[139] Initial silyl transfer to the ynamine yields ynethiolate **96** and ketene imminium ion **97**. Carbon-carbon bond formation yields thioketene **98**, with a subsequent

electrocyclic ring closure leading to cyclobutene **99**. Subsequent reactivity allows access to cyclobutadienes.

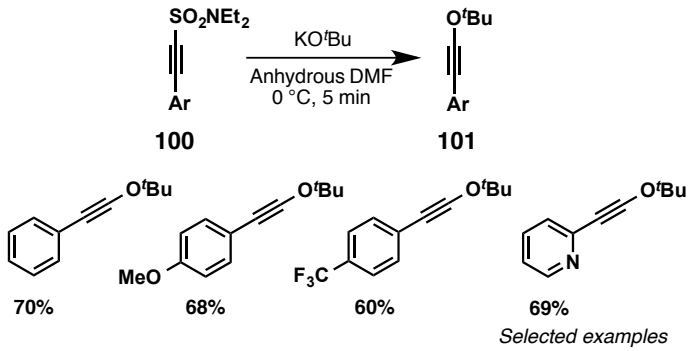


Scheme 82

Alkynyl sulfides represent versatile intermediates in organic chemistry, with the electron-rich nature of the alkyne group often leading to excellent regioselectivity when used in further synthesis. The majority of methods developed towards the synthesis of alkynyl sulfides employ terminal alkynes in combination with an electrophilic sulfur source. The identification of new reaction mechanisms that proceed *via* substrates other than terminal alkynes would therefore greatly improve access to alkynyl sulfides, and in turn allow a greater examination of the reactivity of these understudied substrates.

5. Previous Work Within the Wilden group

Recent work within the Wilden group[140] has identified that potassium alkoxides exhibit a reaction profile considerably more varied than the conventional view of simply behaving as a strong base. For instance, a simple, quick synthesis of synthetically challenging ynol ethers **101** from alkynyl sulfonamides **100** has been achieved *via* a displacement at an *sp*-centre (**Scheme 83**). The products are formed in good yields and show tolerance of a variety of functionalities.



Scheme 83

The reaction was found to exhibit several features that seemed difficult to rationalise. For instance, the reaction was found to only be successful when conducted in DMF, with none of the expected ynol ether observed when carried out in THF, acetonitrile, toluene, dichloromethane or DMSO. With potassium *tert*-butoxide known to increase the rate of decomposition of DMF to form carbon monoxide and *N*,*N*-dimethylamine, the reaction mixture would therefore resemble that often encountered in the recently disclosed transition metal-free biaryl syntheses, that is, a strong base in combination with a secondary amine additive.[141] In addition, the reaction was found to depend critically upon the nature of the alkali metal cation, with no reaction observed for sodium, lithium, magnesium, calcium and aluminium analogues. Again, this is in agreement with the findings from many transition metal-free biaryl coupling procedures, in which potassium *tert*-butoxide is unique in promoting reactivity.

The combination of a potassium alkoxide with a secondary amine additive is extremely common in organic chemistry, especially in the area of transition metal-free chemistry. In addition to the synthesis of biaryl molecules, research in this area has

developed transition metal-free variants of many of the common palladium catalysed processes, particularly Heck reactions.[142,143] However, whilst these reactions are generally accepted to proceed *via* the intermediacy of an aryl radical, formed following an initial single electron transfer, there is often little appreciation of the role of alkoxides beyond behaving simply as strong bases, or partaking in the formation of a complex in combination with an additive. Work in this thesis will initially attempt to provide insight into the role played by both metal alkoxides and additives in transition metal-free biaryl synthesis. With little agreement as to the role played by additives, any contribution to this area would represent a valuable addition to mechanistic understanding. Any knowledge gained may subsequently allow a mechanistic re-evaluation of further processes that proceed only in the presence of a strong base and a secondary amine (**Scheme 83**).

With an understanding of the reaction mixture at hand, efforts will be made to explore the scope of the mechanisms involved in such transition metal-free processes. For instance, the same combination of reagents will be applied to further substrates that, similarly to aryl iodides, are readily able to behave as single electron acceptors. As such, both terminal and internal alkynes will be studied, with the aim of finding *any* evidence to suggest that addition mechanisms proceed by an alternative mechanism to the commonly accepted ionic addition reaction. Whilst target molecules may not be complex, any further insight into the mechanism of reactivity would be extremely interesting from a fundamental perspective, and may also allow access to substrates that commonly require a transition metal catalyst in their synthesis.

Results and Discussion

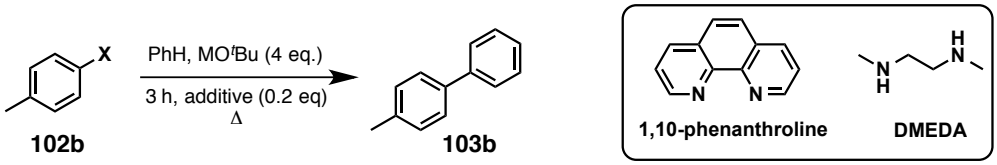
6. Synthesis of Biaryls

In light of the ambiguity surrounding the apparently critical role played by additives in transition metal-free processes, experiments were conducted to try and gain an insight into their mode of reactivity. Intriguingly, Hayashi *et al*.[55] did not report a yield for a control reaction conducted in the presence of potassium *tert*-butoxide alone, despite noting that, in general, the 1,10-phenanthroline mediated reaction proceeded significantly quicker with potassium *tert*-butoxide than its sodium equivalent. The analogous control experiment conducted with sodium *tert*-butoxide gave less than 1% conversion, and less than 1% yield of biaryl as determined by GC. The observed faster rate of reaction in the presence of potassium *tert*-butoxide compared to sodium *tert*-butoxide made this control reaction a logical place to begin.

6.1. Initial Observations and Reaction Scope

As a starting point, two experiments were run in parallel. In sealed tubes, iodobenzene and potassium *tert*-butoxide were stirred in benzene at 150 °C, with or without commercial 1,10-phenanthroline. Surprisingly, upon quenching the reaction after 3 h, crude NMR analysis showed that a significant amount of biphenyl had formed in the reaction without 1,10-phenanthroline. Indeed, a simple comparison of the product integral to remaining iodobenzene integral suggested that a similar amount of biphenyl was formed in the reactions with and without 1,10-phenanthroline. It immediately became apparent that 1,10-phenanthroline, and by extension all other 'ligands', are *not* crucial to the success of biaryl coupling reactions, and that the bulk transformation can be observed in the presence of KO^{t}Bu alone.[144]

Optimisation of the reaction conditions led to the synthesis of 4-methylbiphenyl (**103b**) in 66% yield, comparable to that achieved in the presence of commercial 1,10-phenanthroline (**Table 2, Entries 5** and **13**).



Entry	X	MO^{t}Bu (eq)	Additive	Temp (°C)	Isolated Yield 103b (%)
1	I	K^+ (4)	-	55	0
2	I	K^+ (4)	-	85	0
3	I	K^+ (4)	-	110	3
4	I	K^+ (4)	-	160	38
5[a]	**I**	**K^+ (4)**	**-**	**160**	**66**
6	I	K^+ (2)	-	160	30
7	Br	K^+ (4)	-	160	6
8	Cl	K^+ (4)	-	160	0
9	I	Na^+ (4)	-	160	2
10	I	Li^+ (4)	-	160	0
11	I	Na^+ (4)	1,10-phen	160	65
12	I	K^+ (4)	1,10-phen	85	2
13	**I**	**K^+ (4)**	**1,10-phen**	**160**	**65**
14	I	K^+ (4)	DMEDA	85	53
15	I	K^+ (4)	DMEDA	160	67

[a] Reaction time extended to six hours

Table 2

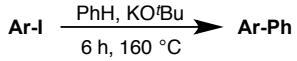
The optimisation of the reaction presented several significant observations, which provide an indication as to the underlying mechanism. Firstly, the coupling reaction seems unique to potassium *tert*-butoxide, with severely diminished or no reactivity observed for the sodium and lithium analogues respectively (**Table 2, Entries 9–10**). The poorer reactivity upon ascending Group 1 alkoxides mirrors the results found by the groups of both Hayashi, and Kwong and Lei. Secondly, there appears to be no advantage in using 1,10-phenanthroline when employing potassium *tert*-butoxide as base (**Table 2, Entries 5** and **13**), but a significant advantage when sodium *tert*-butoxide is used (**Table 2, Entries 9** and **11**). The yield of biphenyl increased from

2% to 65% upon inclusion of 1,10-phenanthroline in the sodium *tert*-butoxide mediated reaction, a value comparable to that achieved with potassium *tert*-butoxide. Reaction efficiency is also significantly diminished on changing from an iodoarene to bromo- and chloro-analogues (**Table 2, Entries 7** and **8**), in agreement with observations made by Hayashi *et al*. and Shi *et al*. The optimum reaction temperature was found to be 160 °C, with little conversion observed below, and significant polymerisation observed above this temperature (**Table 2, Entries 1–4**). Addition of DMEDA appears to allow the reaction to occur with a similar efficiency though under considerably milder conditions (**Table 2, Entry 14**). Despite this, it is clear that additives are not an essential feature of transition metal-free cross-coupling reactions.

With optimised conditions for the cross-coupling in hand, a range of biaryl compounds **103** with varying electron demand could be synthesised to examine the scope of the reaction (**Table 3**).[144]

The reaction is therefore applicable to a range of aryl iodides **102a**–**h**, and biaryl compounds **103a**–**h** may be synthesised in acceptable to good yields. The low yields obtained for some of the compounds may be a result of the high reactivity of intermediate aryl radicals, which could react preferentially *via* hydrogen atom abstraction, and the forcing reaction conditions, with some degree of polymeric material recovered for all reactions. No reaction was observed for 4-cyanoiodobenzene **102i**, possibly due to the instability of the cyano unit under the basic reaction conditions. It is again clear from **Table 3** that, whilst reactions may proceed more efficiently or under milder conditions in the presence of 1,10-phenanthroline, the bulk effect can be observed in the presence of potassium *tert*-butoxide alone. In the presence of DMEDA, however, (**Table 3, Entry 11**), no improvement in yield is observed relative to the ligand free conditions.

Biaryls can therefore be successfully synthesised *inter*molecularly under transition metal-free conditions, without the addition of additives that had previously been reported to be crucial to reactivity.



102a–i **103a–i**

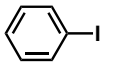
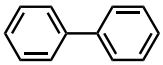
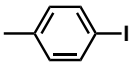
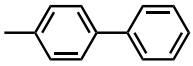
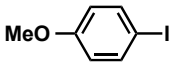
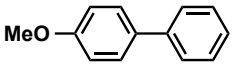
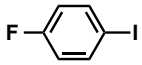
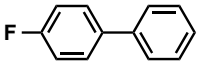
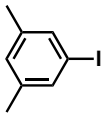
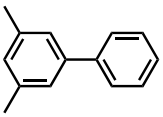
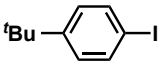
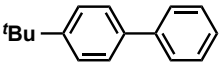
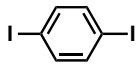
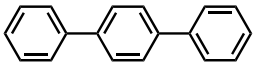
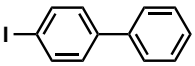
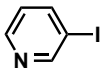
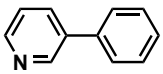
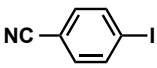
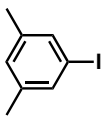
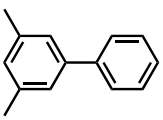
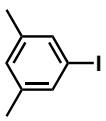
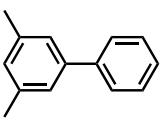
Entry	Ar-X	No.	Additive	Biaryl	No.	Yield (%)
1		**102a**	-		**103a**	77
2		**102b**	-		**103b**	66
3		**102c**	-		**103c**	48
4		**102d**	-		**103d**	64
5		**102e**	-		**103e**	48
6		**102f**	-		**103f**	30
7		**102g**	-		**103ga**	30
					**103gb**	21
8		**102h**	-		**103h**	37
9		**102i**	-	N/A	**-**	-
10		**102e**	1,10-phen		**103e**	81
11		**102e**	DMEDA		**103e**	45

Table 3

6.1.1. The Effect of 1,10-Phenanthroline

Intrigued by the role played by 1,10-phenanthroline, especially in promoting the coupling reaction in the presence of sodium *tert*-butoxide, mechanistic studies were conducted to gain a better understanding.

The 1,10-phenanthroline obtained from a number of commercial sources (Sigma Aldrich and Alfa Aesar) had a slight pink or off-white appearance, even when taken directly from a freshly opened bottle. Given that 1,10-phenanthroline is able to form strong complexes with almost all transition metals,[145] this discolouration may have been the result of transition metal contamination. In addition, the melting point of commercial 1,10-phenanthroline was found to be significantly lower than the literature value of 118 °C,[146] extending over the range 90–99 °C. The observed melting point range matched the literature value for the monohydrated species (97–98 °C).[147] Indeed, the presence of a large amount of water was clearly visible in the ^{1}H NMR spectrum.

Commercial 1,10-phenanthroline was therefore rigorously purified by first converting to the mesylate salt, and then washed with 28% aqueous ammonia solution. Removal of solvent yielded a white solid, which was subsequently purified *via* recrystallisation from chloroform/petrol. The resulting white solid was found to be spectroscopically pure by ^{1}H NMR analysis, and gave an elemental analysis and melting point in good agreement with the literature value (**Table 4**).

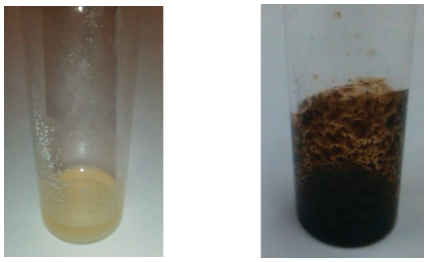
Element	Theoretical (%)	Commercial (m.p. 90–99 °C)	Purified (m.p. 115–116 °C)
C	79.78	72.62	78.09
H	4.47	4.89	4.57
N	15.55	14.12	16.2

Table 4

With highly pure reagent in hand, the coupling reaction of **Table 2** was repeated in the presence of 1,10-phenanthroline, using both commercial and purified additive.

Interestingly, in the case of the purified 1,10-phenanthroline, an immediate, exothermic reaction occurred at room temperature to give a black tar. For commercially sourced 1,10-phenanthroline, a similar colour change was observed at room temperature, though over a period of several minutes.

Repeating the reaction in the absence of an aryl iodide, and with equimolar amounts of potassium *tert*-butoxide and recrystallised 1,10-phenanthroline in THF immediately gave rise to the same, exothermic reaction and black tar formation, even at room temperature. When using commercial 1,10-phenanthroline under otherwise identical conditions, a pale yellow solution was instead observed after five minutes at room temperature (**Figure 5**).



Commercial 1,10-phen | Purified 1,10-phen

Figure 5

The black tar was dissolved in $CDCl_3$ and the ^1H NMR recorded. The signals arising from 1,10-phenanthroline appear almost unchanged. Significantly, however, the characteristic singlet at 1.2 ppm associated with the *tert*-butyl group was found to have collapsed from the expected integral of nine, to an integral of less than one, showing that almost complete destruction of the *tert*-butyl unit had occurred (**Figure 6**).

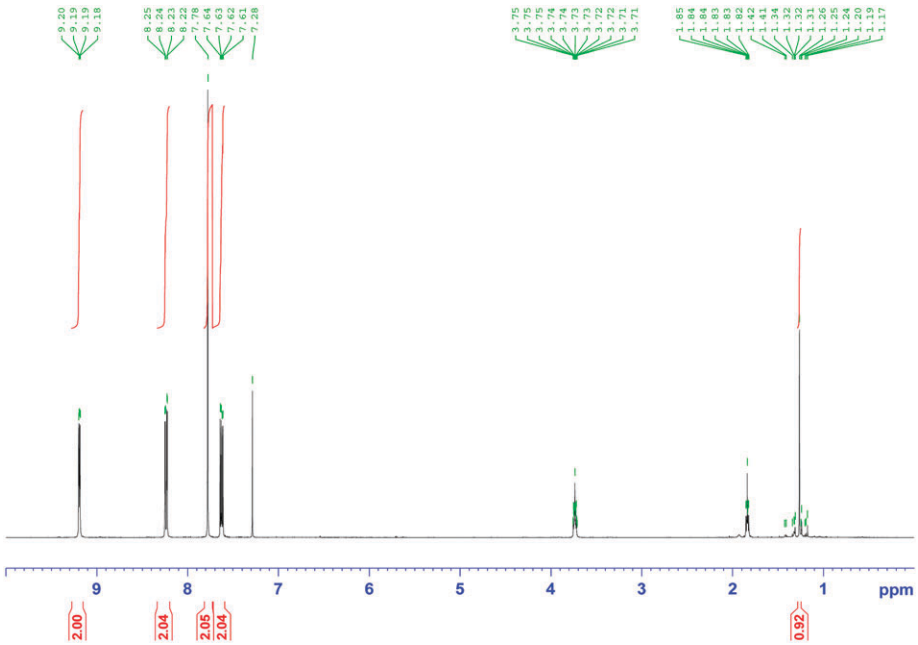


Figure 6

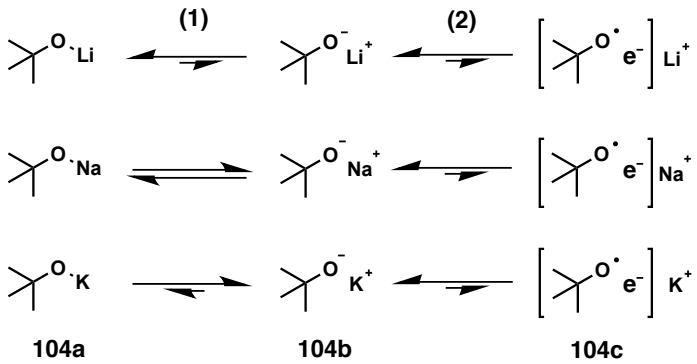
Hayashi *et al*.[55] and others have presented 1,10-phenanthroline as behaving simply as a bidentate ligand, forming a complex with sodium or potassium *tert*-butoxide, analogously to the established behaviour with transition metals. Single electron transfer then occurs from this complex, initiating the coupling reaction. This seems unlikely for several reasons. Firstly, Popov *et al*.[148] have utilised NMR resonances to determine that, on descending the Group 1 cations, binding efficiencies with bipyridine complexes decrease dramatically, a result of increasing cationic radius (Li^+ = 0.60 Å, Na^+ = 0.97 Å, K^+ = 1.33 Å).[149] Kaim, who used a lack of alkali metal splitting in EPR spectroscopy to determine that the association between ligand and potassium cation is not close, has echoed this result.[150] 1,10-Phenanthroline forms particularly strong complexes with first row transition metals, with complex stability following the established Irving Williams series (Fe(II) < Co(II) < Ni(II) < Cu(II), ionic radii 0.76–0.72 Å).[151] As such, the most efficient complexation of Group 1 alkoxide and 1,10-phenanthroline would be expected when using lithium *tert*-butoxide in the coupling reaction. However, no biaryl product was observed in the presence of LiO^tBu and 1,10-phenanthroline (**Table 1, Entry 10**). Secondly, the complete destruction of potassium *tert*-butoxide upon exposure to rigorously purified 1,10-phenanthroline suggests that the ligand in fact plays a destructive role in the reaction, rather than behaving as a bidentate ligand.

6.2. Mechanistic Studies

6.2.1. Alkoxide Dissociation

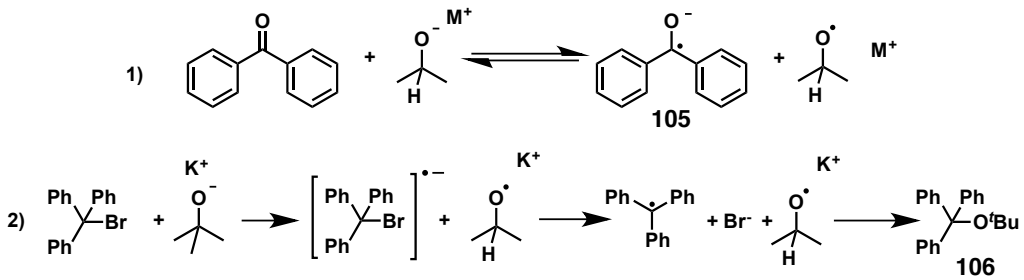
DFT modelling carried out previously in the group has shown that potassium *tert*-butoxide provides an essentially dissociated source of *tert*-butoxide anions.[140] This is in contrast to sodium and lithium *tert*-butoxides, in which shorter bond lengths (2.05–1.70 Å) indicate a significant degree of covalent character between the Group 1 metal and oxygen atom. Significantly, severely diminished or no reactivity was observed for sodium and lithium *tert*-butoxides respectively (**Table 2, Entries 10** and **11**). In the case of potassium *tert*-butoxide, a bond length of 2.46 Å indicates little covalent character in the bond, and analysis of the charge distribution indicates the formation of a charge-separated species. The additive-free coupling reaction proceeds efficiently only in the presence of potassium *tert*-butoxide, and so the presence of a large concentration of *tert*-butoxide anions suggests that metal alkoxide dissociation may be crucial to reactivity.

A model accounting for this observed difference in reactivity between Group 1 alkoxides takes into account two proposed equilibria (**Scheme 84**). In the first case, the covalently bonded metal alkoxides **104a** are in equilibrium with the charge separated, ionic species **104b**. Upon moving down the Group 1 alkoxides, a greater degree of ionic character is observed. Hence, lithium and potassium *tert*-butoxide represent the two extremes, existing as an essentially covalently bonded species, and an essentially ionic species respectively. Sodium *tert*-butoxide has a bond character intermediate between the two extremes.



Scheme 84

A second equilibrium exists between the charge-separated species **104b** and a species bearing a loosely bound electron, **104c**. The position of the second equilibrium lies heavily to the charge separated species. At sufficiently high temperatures, the loosely bound electron may be transferred to an aryl iodide, generating a radical anion. This single electron transfer behaviour of alkoxides is known in the literature. For instance, by using a combination of EPR spectroscopy and cyclisable radical probes, Ashby *et al*. have shown that alkoxides are able to transfer a single electron to 1) aromatic ketones to form ketyls[15] **105** and 2) alkyl halides to give substitution products[14] **106** (**Scheme 85**). Over a 60-hour period, the reaction of potassium *tert*-butoxide with benzophenone generated benzophenone ketyl **105** in a high relative concentration of 3% (compared to the concentration of ketone), succinctly demonstrating the inherent electron transfer capabilities of alkoxides.



Scheme 85

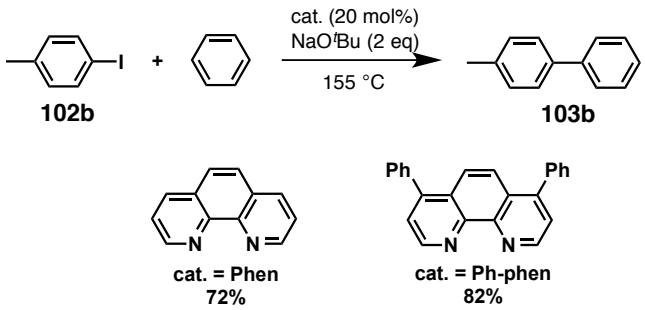
When fully dissociated into the charge-separated species **104b**, Group 1 alkoxides are therefore able to behave as single electron transfer agents. Electron transfer from *tert*-butoxide anions to aryl iodides and the formation of a radical anion would therefore seem to be the logical initiation step of the reaction. Such an electron transfer is extremely endothermic,[69] hence necessitating the high temperatures used. Indeed, a similar conclusion was recently reached by Patil, who studied the electron transfer step in the absence of additives computationally.[73] The author also suggests that the excess of potassium *tert*-butoxide used would likely lead to a complexation between a potassium cation and aryl iodide *via* cation-pi interaction, facilitating the electron transfer step.

The presence of radical intermediates has been confirmed by the inclusion of common radical inhibitors. Pleasingly, the inclusion of one equivalent of the radical scavenger

TEMPO completely attenuated the reaction, mirroring the findings of previous transition metal-free biaryl syntheses.

6.2.2. Role of 1,10-Phenanthroline

It can be seen from **Table 2** that there is little advantage in employing 1,10-phenanthroline when potassium *tert*-butoxide is used as base, but a significant advantage when sodium *tert*-butoxide is the base. As a general class of compounds, phenanthroline derivatives are electron deficient and highly conjugated, and are characterised by two low-lying unoccupied molecular orbitals. As such, phenanthroline derivatives are readily reduced *via* single electron transfer from, for example, alkali metals and organometallics such as Grignard reagents.[150] The effect of this may be seen in the work of Hayashi *et al*., who used phenanthroline derivatives with an increased degree of conjugation (Ph-Phen), and hence a lower lying LUMO, to demonstrate an improved reaction efficiency (**Scheme 86**).[55] The ease with which 1,10-phenanthroline can be reduced *via* single electron transfer immediately raises the suspicion that the molecules are able to behave as temporary electron sinks, accepting an electron from alkoxides, before transferring the electron to aryl iodides.



Scheme 86

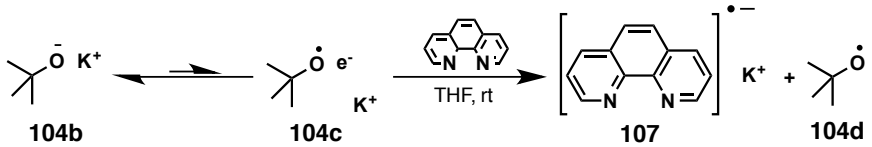
When considering the equilibria of **Scheme 84**, the addition of 1,10-phenanthroline would therefore be expected to accept the loosely bound electron, forming a phenanthroline radical anion and a free *tert*-butoxy radical. Applying Le Chatelier's principle, this would drive the second equilibrium to the right by removing the loosely bound electron. For potassium and sodium *tert*-butoxides, the addition of 1,10-phenanthroline would therefore render the second equilibrium irreversible, and lead to an increase in the concentration of the species bearing the loosely bound electron.

Clearly, the effect of this can be observed in **Table 2**, where the yield of biaryl obtained under sodium *tert*-butoxide mediation increases from 2% in the absence of 1,10-phenanthroline, to 65% in its presence. In the presence of NaO^{t}Bu and 1,10-phenanthroline, there is a sufficient concentration of species **104c** to allow coupling to readily occur. In the case of potassium *tert*-butoxide a sufficient concentration of **104c** exists in the absence of 1,10-phenanthroline to allow reaction to occur. However, addition of 1,10-phenanthroline and the subsequent increase in concentration of species **104c** allows reactions to become viable at milder temperatures. For lithium *tert*-butoxide, the initial equilibrium is such that the molecule exhibits essentially covalent bonding, and so the concentration of charge separated species is insufficient to establish the second equilibrium, even in the presence of 1,10-phenanthroline. Hence, no biaryl is observed under any conditions tested.

Recently, Lei *et al*.[72] have provided evidence of the transfer of an electron between potassium *tert*-butoxide and 1,10-phenanthroline. EPR and cyclic voltammetry were used to demonstrate the formation of a phenanthroline radical anion, and alkoxy radical species, in accordance with the above findings. In addition, Lei *et al*. have used electrochemistry to demonstrate the transfer of an electron from phenanthroline radical anions to aryl halides, strongly supporting the role of phenanthroline as a temporary store of electrons.

6.2.3. Fate of Alkoxy Radical

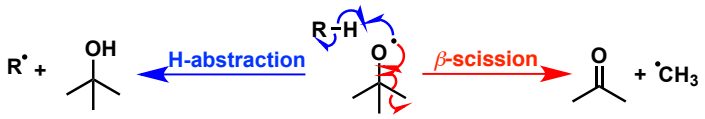
Upon single electron reduction of 1,10-phenanthroline by a Group 1 alkoxide (or alternatively, the transfer of an electron directly to an aryl iodide in the presence of potassium *tert*-butoxide), a free alkoxy radical **104d** remains (**Scheme 87**). It was hypothesised that identifying the decomposition products of this radical would lend considerable weight to the proposed mechanism.



104b 104c 107 104d

Scheme 87

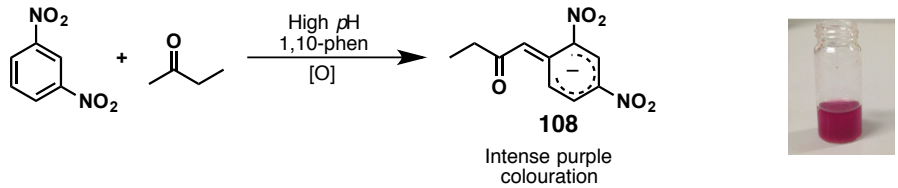
Depending on the reaction conditions, free *tert*-butoxy radicals may be expected to undergo a number of well-established radical decomposition processes; 1) abstraction of a hydrogen atom from the reaction mixture to form *tert*-butanol and a new radical species; 2) *β*-scission to form acetone and methyl radicals (**Scheme 88**).[152]



Scheme 88

It is believed that uncontrolled reactions of the highly reactive methyl radicals may have given rise to the polymeric material and dark brown colour observed in each reaction.

Upon mixing an equimolar amount of potassium *tert*-pentoxide and 1,10-phenanthroline in THF, butanone was found to be a major product component *via* mass spectrometry analysis. Further evidence for the existence of a ketone product was obtained by employing the Janovsky test for enolisable ketones.[153] A strong colour change from light brown to purple was immediately observed upon the addition of a small amount of sodium hydroxide to a dilute THF solution of *m*-dinitrobenzene, potassium pentoxide and 1,10-phenanthroline. The colour change is characteristic of a positive result in the Janovsky test, and indicates that enolisable ketones make up a substantial proportion of the reaction mixture (**Scheme 89**). By extension, free alkoxy radicals must form a major part of the reaction mixture in biaryl coupling reactions.

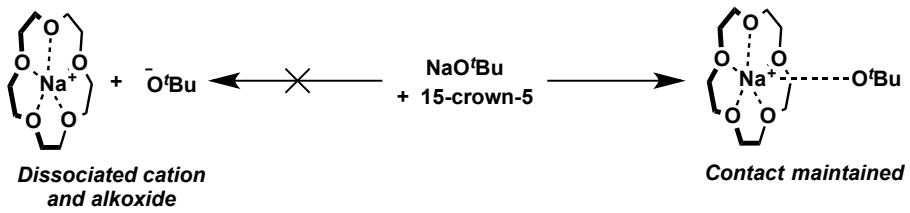


Scheme 89

6.2.4. Sodium *tert*-Butoxide

In keeping with the hypothesis discussed so far, the degree of dissociation of the metal alkoxide is crucial to the success of the reaction. In order to increase the degree of

dissociation of the sodium analogue and hence switch on the coupling reaction, it was hypothesised that crown ethers could be used to complex the metal cation, ensuring complete dissociation of the alkoxide. An increased concentration of the charge-separated species would in turn lead to a greater concentration of the species **104c** bearing a loosely bound electron, and allow the coupling reaction to proceed as for potassium *tert*-butoxide. 15-crown-5 was chosen to ensure optimum size matching with the sodium cation (cavity diameter = 1.70–2.20 Å, Na^+ diameter = 1.90 Å).[154]



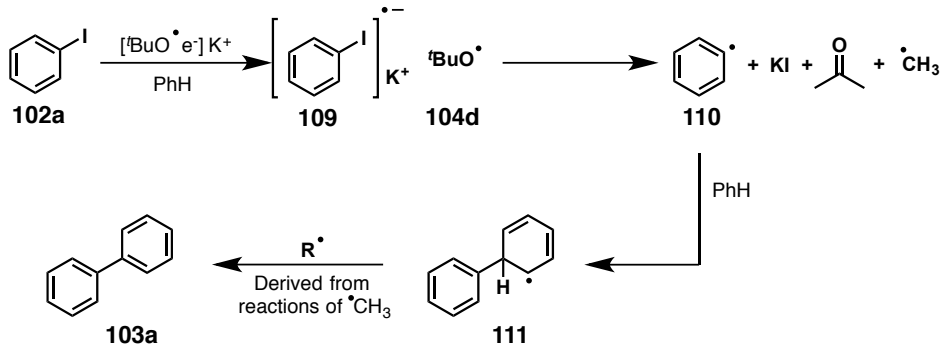
Scheme 90

Disappointingly, the inclusion of 15-crown-5 had no effect on the biaryl yield when mediated by sodium *tert*-butoxide, with the yield remaining at 2%. However, it is known that in the presence of a highly coordinating anion such as *tert*-butoxide, simple stoichiometric mixtures of crown ether and metal alkoxides retain a contact between the metal and alkoxide (**Scheme 90**).[155,156] Hence, the inclusion of a crown ether would not necessarily be expected to lead to an increase in alkoxide anion concentration, and so may not be expected to improve the yield of the biaryl product. In future experiments, a cryptand could be used to ensure complete separation of cation and alkoxide.

6.3. Mechanism

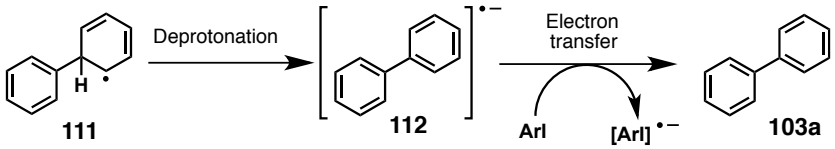
A mechanism for the additive-free coupling reaction can be proposed (**Scheme 91**), and is initiated by single electron transfer from alkoxides to aryl iodides. The iodoarene radical anion **109** that is initially formed rapidly dissociates to iodide and an aryl radical **110**. The resulting alkoxy radical decomposes *via β*-scission to yield acetone and methyl radicals. Addition of the aryl radical to aromatic solvent generates cyclohexadienyl radical **111**, which generates biaryl **103a** upon rearomatisation. The mechanism by which the rearomatisation occurs has been much discussed. Though radical abstraction as shown in **Scheme 91** is plausible under the reaction conditions,

it requires a termination step between two transient intermediates, an inherently unfavoured reaction owing to the low respective concentrations.



Scheme 91

Alternatively, Studer and Curran[58] have suggested that deprotonation of cyclohexadienyl radical **111** under the strongly basic conditions would generate a radical anion **112** (**Scheme 92**). **112** would be expected to be a powerful reducing agent, which can regain aromaticity upon electron transfer to a molecule of aryl iodide *via* an outer-sphere pathway, hence completing the radical cycle. Wayner *et al*. have shown previously that an electron transfer from aryl radical anions is able to reduce alkyl halides.[157] The strongly basic reaction conditions make this pathway inherently more likely than an alternative of electron transfer from **111** to a second molecule of aryl iodide to generate a cation, followed by proton transfer.

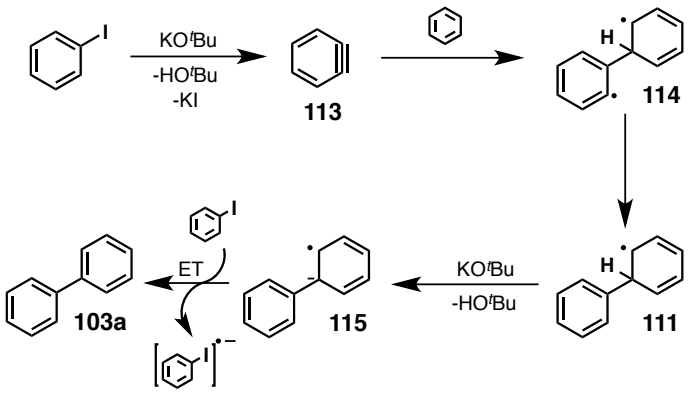


Scheme 92

6.3.1. A Benzyne Intermediate?

Murphy *et al*. have suggested that, in the absence of 1,10-phenanthroline, coupling reactions proceed *via* a benzyne intermediate **113** (**Scheme 93**). The benzyne behaves as a diradical, generating diradical intermediate **114** upon addition to benzene.[158] Hydrogen atom abstraction from the solvent, benzene, followed by deprotonation

under the strongly basic conditions would yield radical anion **115**, which, upon electron transfer to a further aryl halide, generates the expected biphenyl **103a**.

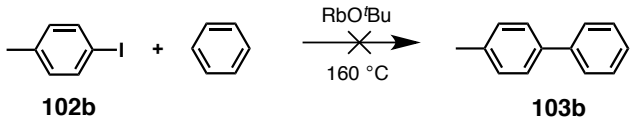


Scheme 93

Indeed, benzyne intermediates have been invoked previously by Daugulis *et al*. to account for *intra*molecular cyclisations of aryl bromides in the presence of potassium *tert*-butoxide alone.[159] In an attempt to disprove this theory, the cross-coupling was repeated with pentafluoroiodobenzene. The size of the fluorine atom should ensure that steric effects do not prevent cross-coupling occurring. Unfortunately, no coupled product was observed either with or without 1,10-phenanthroline, with only starting material recovered. This may have been due to the extremely electron deficient nature of the ring compared to successful substrates (**Table 3**). Nevertheless, there remain two problems with the benzyne proposal. Firstly, coupling products were formed as a single regioisomer with respect to the aryl halide. This is in common with the ligand promoted couplings of Hayashi *et al*., Kwong and Lei *et al*. and Shi *et al*. A reaction proceeding *via* a benzyne intermediate would be expected to yield at least some proportion of regioisomers. Whilst it is feasible that only a trace amount of benzyne formation is required to initiate the reaction, after which standard homolytic aromatic substitution dominates, this seems unlikely in this case. Secondly, in the absence of 1,10-phenanthroline, Murphy *et al*.[76] have reported a trace of coupling product from the reaction of 2,6-dimethyliodobenzene. This clearly cannot form *via* a benzyne pathway, and so an alternative mechanism requiring electron transfer to the aryl iodide must be in operation.

6.4. Alternative Alkoxides

On descending the Group 1 alkoxides, a greater degree of separation of metal cation and alkoxide is clearly observed. By extending this principle, the lower members of the Group 1 metals might be expected to show an even greater degree of dissociation, and hence a greater concentration of the alkoxy radical species **104c** (**Scheme 84**). Reactions conducted with either caesium or rubidium *tert*-butoxide may therefore be expected to give access to biaryls at considerably milder temperatures. As such, in combination with collaborators, rubidium *tert*-butoxide was synthesised *via* treatment of *tert*-butanol with the parent metal under inert conditions. Unfortunately, use of rubidium *tert*-butoxide in place of potassium *tert*-butoxide led to none of the expected biaryl product **103b**, even under forcing conditions, with **102b** recovered unchanged (**Scheme 94**).



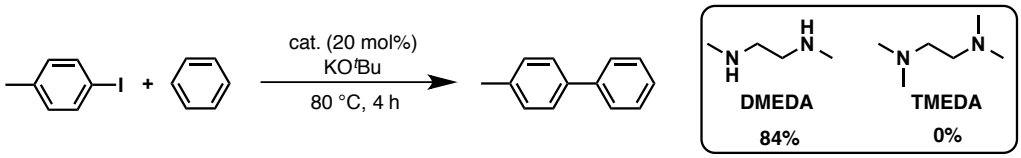
Scheme 94

This may have been due to the extremely hydroscopic nature of the Group 1 alkoxides, and especially rubidium *tert*-butoxide, with traces of water in the reaction mixture preventing the radical formation. In future, freshly sublimed rubidium *tert*-butoxide may give ready access to biaryls under mild reaction conditions.

6.5. Alternative additives

6.5.1. Role of DMEDA

Whilst the role of 1,10-phenanthroline has been thoroughly investigated, the role played by alternative 'ligands' such as DMEDA in reaction initiation remains less well understood. One feasible role of DMEDA is simply to act as a hydrogen bond donor, which is able to stabilise the transient alkoxy radical species, and so promote single electron transfer. The necessity of a free N-H unit has been succinctly demonstrated by Kwong and Lei *et al*.[56] in contrasting the relative efficiencies of DMEDA and TMEDA (**Scheme 95**).

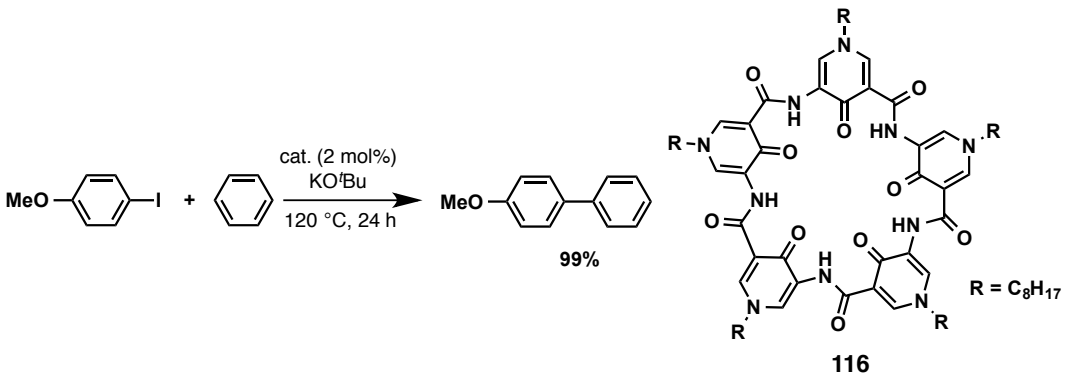


Scheme 95

A hydrogen bond donor would be able to stabilise an oxygen centred radical species, and hence draw the second equilibrium of **Scheme 84** to the right. Such stabilisation of alkoxy radicals has precedent in the literature, with Guerra *et al.*[160] demonstrating a significant stabilisation of phenoxy radicals in the presence of hydrogen bond donor solvents such as hexafluoropropanol.

6.5.2. Further Additives

Numerous molecules, often structurally unrelated to phenanthroline derivatives, have been reported to behave as efficient mediators of the biaryl coupling reaction. Several of the promoters share common elements such as electron deficient or extended aromatic units, resulting in low lying LUMOs that can readily accept an electron. Many authors have neglected to speculate as to the role of these additives beyond acting as conventional multidentate ligands. For instance, Zeng *et al.*[65] have recently proposed a pyridine pentamer **116** (**Scheme 96**), able to mediate the coupling reaction and generate biaryls in excellent yields.

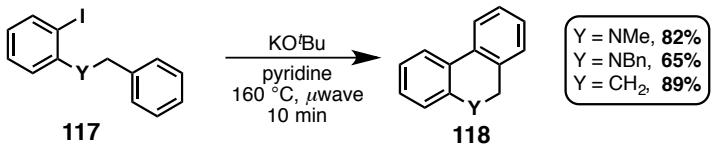


116

Scheme 96

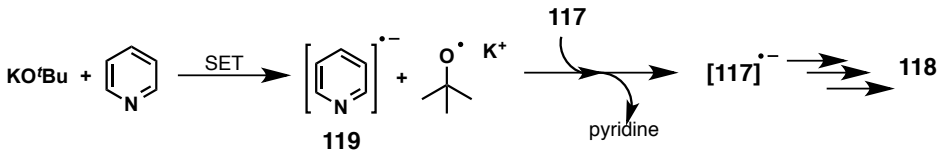
Drawing analogy with the role played by 1,10-phenanthroline would envisage these additives behaving simply as temporary electron sinks, able to readily accept an electron, before transfer to an aryl iodide.

Similar to the work presented here, Charette *et al*.[161] have disclosed an *intra*molecular arylation reaction of aryl iodide **117** that can proceed in the presence of potassium *tert*-butoxide alone to give cyclised products **118**. No mediation by a phenanthroline or secondary amine additive is required. The workers noted many of the same observations made in this work, including the superiority of potassium *tert*-butoxide compared to the sodium salt, and also propose that the reaction proceeds *via* an initial single electron transfer. Successful reactions employed an excess of potassium *tert*-butoxide in pyridine, under microwave irradiation (**Scheme 97**).



Scheme 97

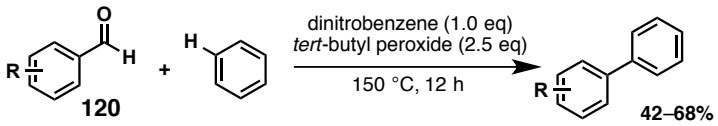
Although the authors note a fundamental lack of understanding concerning the mode of radical generation in the absence of phenanthroline derivatives, the electron deficient nature of pyridine makes it possible in this case that pyridine is fulfilling the role of a temporary sink of electrons. Single electron transfer from potassium *tert*-butoxide to pyridine generates a radical anion **119**, which is subsequently able to transfer an electron to the aryl iodide (**Scheme 98**). The pyridine radical anion has been well studied, and is readily formed upon single electron transfer from, for example, alkali metals[162] and LDA.[163]



Scheme 98

In addition, Yang *et al*.[164] have recently divulged a transition metal-free method towards biaryl formation *via* the decarbonylation of aromatic aldehydes **120** (**Scheme 99**). In this instance, an excess of 1,2-, 1,3- or 1,4-dinitrobenzene is used in combination with di-*tert*-butyl peroxide to form biaryls in moderate to good yields. The authors speculate that, similarly to the role proposed in this work for 1,10-

phenanthroline, dinitrobenzene acts as a sink of electrons, facilitating transfer between the cyclohexadienyl species and di-*tert*-butyl peroxide.



Scheme 99

To further investigate this hypothesised role of additives, the coupling reaction was conducted in the presence of C_{60}, a known single electron acceptor.[165] Previous work within the group has shown, *via* EPR analysis, that electron transfer occurs from a mixture of potassium *tert*-butoxide and secondary amine, to C_{60}.[166] Unfortunately, conducting the reaction of **Table 2** with 20 mol% of C_{60} did not yield any of the expected biaryl, with starting material instead recovered. C_{60} appeared to be only poorly soluble in benzene, though attempts to improve the solubility *via* amine functionalisation again failed to yield any biaryl product. One possible explanation is that, whilst able to readily accept an electron, C_{60} is unable to subsequently transfer the electron to an aryl iodide, hence preventing reaction initiation and terminating the reactivity.

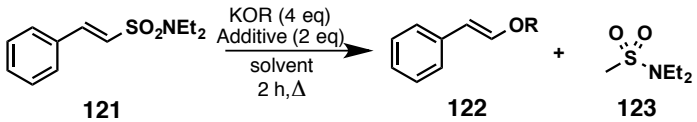
The coupling of iodoarenes with aromatic rings has therefore been achieved in the absence of transition metal catalysis, and phenanthroline or diamine ligands, previously reported to be crucial to reaction success. Whilst reactivity is undoubtedly slightly more efficient in the presence of such additives, the bulk transformation can be observed in their absence. The most important factor determining reactivity appears to be the degree of dissociation of the Group 1 alkoxide used. Upon descending the Group 1 alkoxides, a greater degree of ionic character is exhibited, with subsequent increased reactivity observed.

7. Terminal Alkynes and the Synthesis of Enol Ethers

Although the synthesis of biaryls has shown that potassium alkoxides are able to behave as single electron transfer agents in the absence of an additive, the combination of an alkoxide with either a secondary amine or 1,10-phenanthroline is clearly a potent source of reducing power. The combination of reagents was therefore applied to further substrates with the aim of identifying underlying mechanistic pathways. Particularly interesting was the prospect of using the potassium alkoxide/additive mixture to identify substrates that have the potential to react *via* a $S_{RN}1$ mechanism.

7.1. Reactions of Alkenes

Sulfonamide derivatives have been used previously within the group, and so as a starting point, sulfonamide-substituted styrene derivative **121** was investigated (**Table 5**). **121** may be formed in high yield as a single isomer simply upon addition of *N*,*N*-diethylamine to *trans*-*β*-styrenesulfonyl chloride.



121 **122** **123**

Entry	R	Additive	Solvent	Temp. (°C)	Product yield
1	*t*Bu	DMEDA	THF	50	**123** (28%)
2	*t*Bu	-	THF	100	**123** (31%)
3	Me	-	THF	80	**121** (78%), **122** (11%), **123** (18%)
4	Me	1,10-phen	THF	100	**122** (31%), **123** (7%)
5	Me	1,10-phen	THF	rt	**121** (85%), **123** (3%)
6	Me	1,10-phen	THF	80	**122** (50%), **123** (8%)
7[a]	Me	1,10-phen	THF	80	**122** (61%), **123** (10%)
8	Me	1,10-phen	DMF	rt (15 h)	**122** (54%), **123** (3%)
9	Me	-	DMF	rt (15 h)	**122** (63%), **123** (3%)

[a] Reaction conducted in sealed tube that had not been back flushed with argon

Table 5

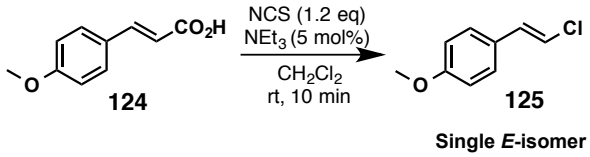
In the presence of potassium *tert*-butoxide, cleavage of the alkene of **121** had occurred, clearly demonstrated by the isolation of **123** in 28% yield (**Table 5**, **Entry 1**). Similar bond cleavage has been previously reported by Julia *et al*. during investigations into the reaction of potassium alkoxides with analogous *E*-styryl phenyl sulfones.[167] However, no further products could be isolated, presumably due to the instability of any *tert*-butyl substituted enol ether (**122**) that may have formed. Carbon-carbon bond cleavage could therefore occur in the presence of potassium *tert*-butoxide alone (**Table 5**, **Entry 2**), drawing parallels with findings from biaryl syntheses.

Upon changing to potassium methoxide, a small amount of the expected enol ether **122** was formed (**Table 5**, **Entry 3**). This was significantly increased to 31% upon the inclusion of two equivalents of 1,10-phen (**Table 5**, **Entry 4**). An improvement in yield in the presence of 1,10-phen, a molecule shown previously to assist in the initiation of electron transfer reactions when combined with a potassium alkoxide, indicates that a single electron transfer mechanism could be a competing pathway in this instance. However, such an isolated piece of evidence allows little certainty. Careful control of the reaction temperature allowed the yield of **122** to increase to 50% (**Table 5**, **Entry 6**), whilst a small improvement in yield was also observed when the reaction was conducted under an atmosphere of air (**Table 5, Entry 7**). This improvement in yield may have been due to the presence of a proton donor (in this case, H_2O or trace methanol), with the presence of small amounts of an alcohol known to improve yields of certain alkoxide-mediated transition metal-free processes.[142]

Changing solvent to DMF allowed the reaction to proceed under considerably milder conditions, with 54% of **122** isolated following overnight stirring at room temperature (**Table 5**, **Entry 8**). Interestingly, in the absence of 1,10-phen, an improved yield of 63% was observed (**Table 5**, **Entry 9**). The well-known decomposition of DMF in the presence of alkoxide bases generates carbon monoxide and *N*,*N*-dimethylamine.[168] In this case, the secondary amine may behave analogously to DMEDA in biaryl coupling reactions, hence removing the requirement for 1,10-phenanthroline.

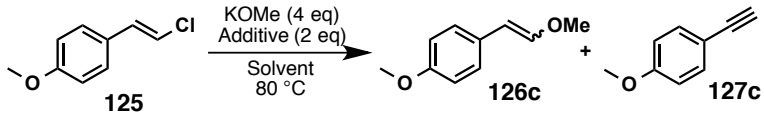
Simultaneously, *E*-1-(2-chloroetheneyl)-4-methoxybenzene (**125**) was synthesised as a single geometrical isomer *via* a Hunsdiecker reaction of the parent α,β-unsaturated

carboxylic acid **124** (**Scheme 100**).[169] Though forming **125** in 91% yield, the chlorination reaction was limited to electron rich aromatic systems.



Scheme 100

Chlorostyrene **125** was then submitted to the same reaction conditions as determined for alkenyl sulfonamide **121**.



Entry	Additive	Solvent	Time (h)	Product	126c (*Z*:*E*)
1	-	THF	2	**125** (100%)	-
2	1,10-phen	THF	2	**125** (72%), **126c** (8%)	9:91
3	1,10-phen	THF	15	**125** (39%), **126c** (24%), **127c** (28%)	9:91
4[a]	1,10-phen	THF	15	**125** (12%), **126c** (20%), **127c** (20%)	10:90
5	1,10-phen	DMF	15	**126c** (42%), **127c** (25%)	55:45
6[a]	1,10-phen	DMF	15	**126c** (26%)	65:35

[a]10 equivalents KOMe used

Table 6

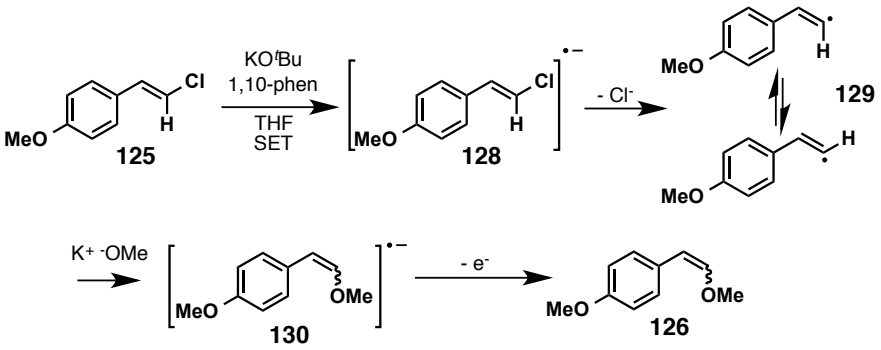
Formation of enol ether **126c** required slightly more forcing conditions compared to the use of alkenyl sulfonamide **121**. The presence of 1,10-phen was found to be crucial to the success of the reaction, with only starting material recovered in its absence (**Table 6**, **Entry 1**). A small amount of **126c** was formed after 2 hours upon reacting alkenyl chloride **125** with potassium methoxide and 1,10-phen (**Table 6**, **Entry 2**).

Allowing the reaction to continue for a longer time increased the yield of **126c** to 24%, with an *E*:*Z* ratio of 9:91 determined *via* ^{1}H NMR integral comparison (**Table 6**, **Entry 3**). Little difference in yield or *E*:*Z* ratio was observed when an increased number of methoxide equivalents were used (**Table 6**, **Entry 4**). Interestingly, a change of solvent to DMF resulted in a reversal of *E*:*Z* selectivity, with a slight *Z*-preference observed under otherwise identical reaction conditions (**Table 6**, **Entry 5**). Increasing the equivalents of potassium methoxide used emphasised this reversal in selectivity, with a *Z*:*E* ratio of 65:35 observed (**Table 6**, **Entry 6**).

At this juncture, it was important to determine if the enol ethers arose simply from an elimination-addition reaction *via* alkyne **127c**. As such, commercially obtained **127c** was used in place of **125**. Conducting the reaction in DMF, **126c** was synthesised with a *Z*:*E* ratio of 83:17, with the selectivity in agreement with that observed for the synthesis of **126** from **125** in DMF. Elimination of HCl and formation of a terminal alkyne prior to the addition of an alkoxide is therefore likely to be the dominant reaction mechanism in DMF. For the reaction conducted in THF however, no addition product was observed, and the starting alkyne **127c** was recovered unchanged. Whilst an elimination of HCl clearly occurs, as evidenced by the isolation of alkyne **127c** (**Table 6**, **Entries 3** and **4**), subsequent addition of an alkoxide is not the dominant pathway towards enol ether **126c** in THF. Different mechanisms clearly predominate when the reaction is carried out in THF or DMF, as demonstrated by the reversal in *E*:*Z* selectivity.

With the combination of potassium alkoxide and 1,10-phenanthroline known to transfer single electrons to suitable substrates, a feasible reaction pathway would be the $S_{RN}1$ mechanism (**Scheme 101**), proceeding *via* an intermediate vinyl radical. Initial single electron transfer generates radical anion **128**, which rapidly dissociates to give vinyl radicals *E*- and *Z*-**129**. Vinyl radicals have been shown to have a bent geometry, which undergoes rapid inversion owing to a low barrier to inversion.[170] A mixture of *E*:*Z* isomers would therefore be expected, with the ratio dependent on the rate of inversion and radical capture. Attack of **129** by methoxide generates radical anion **130**, which is able to transfer an electron to a second molecule of **125**, forming **126** and completing the radical chain reaction. However, as Galli and Rappoport observed, the unambiguous identification of a reaction undergone by vinylic halides

as a pure $S_{RN}1$ process is difficult, with a diverse number of substitution mechanisms potentially operating in competition.[171]



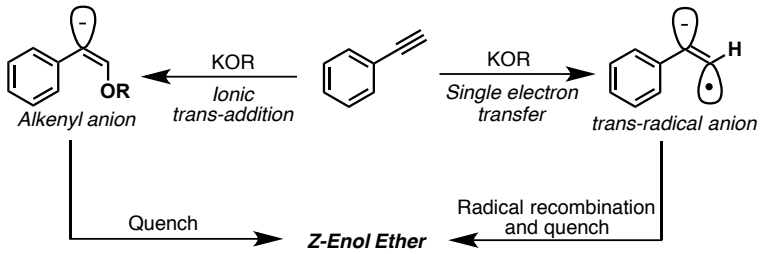
Scheme 101

Attempts to identify a potential $S_{RN}1$ mechanism in the reactions of sulfonamide- or chloro-substituted alkenes with potassium alkoxides were therefore significantly complicated by the number of possible competing reactions, which may include, amongst others, ionic elimination-addition and addition-elimination reactions. The reversal of selectivity observed when changing solvent (**Table 6**, **entries 3**, **5**) highlights the difficulties faced in examining reaction mechanisms. Whilst improvements in reaction yields were observed when using both **121** and **125** in the presence of 1,10-phenanthroline, this alone can not be used to indicate a pathway proceeding *via* single electron transfer. In light of this difficulty, focus was moved to examine the mode of addition of alkoxides to terminal alkynes such as **127c**, formed as an intermediate in the reactions of **125** (**Table 6**, **entries 3–5**).

7.2. Reactions of Terminal Alkynes

Despite the fundamental importance of the reaction products, the addition of alkoxides to terminal alkynes is poorly described from a mechanistic standpoint, with no suitable model to account for observed product distribution. The addition reaction to give an *anti*-Markovnikov product has generally been ascribed to an ionic mechanism. A general rule of *trans*-addition has been suggested[104] to account for the high *Z*-selectivity of products, with reactions proceeding *via* an intermediate alkenyl anion that is subsequently protonated (**Scheme 102**, left). With previous work suggesting that alkoxides have an inherent electron transfer ability, especially when in the

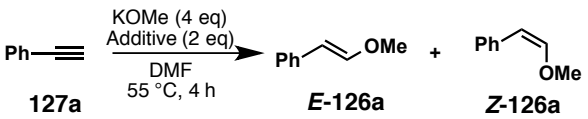
presence of a secondary amine additive, an alternative mechanism proceeding *via* a *trans*-disposed alkenyl radical anion (analogous to the intermediate in dissolving metal reductions of alkynes) would seem plausible (**Scheme 102**, right). Following radical recombination and quenching by a proton source, the *trans*-radical anion would also be expected to selectively give rise to a *Z*-enol ether, making identification of the precise mechanism complex. An electron transfer mechanism could therefore reasonably be invoked to account for the products observed in a reaction that is generally assumed to proceed *via* an ionic addition step. Therefore, *any* evidence to suggest the participation, or indeed exclusivity, of an electron transfer mechanism would be significant from a position of fundamental mechanistic understanding.



Scheme 102

7.2.1. Optimisation and Scope

In an attempt to improve the understanding of the dominant mechanism of **Scheme 102**, the reactions of various terminal alkynes with potassium methoxide and additives were investigated.



Entry	Additive	Combined Yield (%)	*Z*:*E*
1	-	40	65:35
2	DMEDA	56	66:34
3	1,10-Phen	30	55:45
4[a]	DMEDA	70	68:32

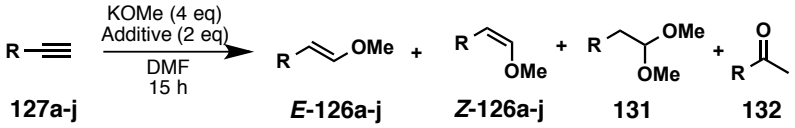
[a] Reaction time extended to 15 h

Table 7

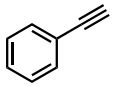
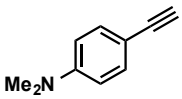
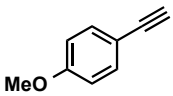
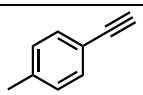
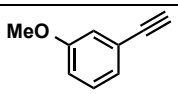
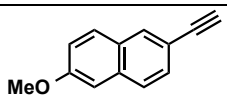
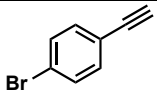
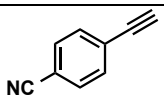
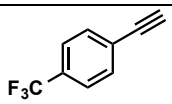
Potassium methoxide was found to add to phenylacetylene in an *anti*-Markovnikov fashion, to yield enol ethers *E*-**126a** and *Z*-**126a** in 40% yield, selective for the *Z*-isomer (**Table 7**, **Entry 1**). With the knowledge that electron transfer mechanisms involving potassium alkoxides may be assisted by the presence of additives, the effects of DMEDA and 1,10-phenanthroline were also investigated. In the presence of DMEDA, a significant increase in yield was observed, together with a similar *Z*:*E* ratio (**Table 7**, **Entry 2**). The use of 1,10-phenanthroline, however, led to a lower yield of 30%, and *Z*:*E* selectivity approaching 1:1 (**Table 7**, **Entry 3**). In common with the destructive role observed of phenanthroline derivatives in the synthesis of biaryls, it again seems in this case that 1,10-phenanthroline has an inhibitory effect on the predominant reaction mechanism. Extending the reaction time to 15 hours improved the yield in the presence of DMEDA to 70%, whilst maintaining the *Z*-selectivity.[172]

As the products observed in the reaction of **127a** with potassium methoxide could be accounted for by either an ionic or single electron transfer mechanism (**Scheme 102**), the reaction was extended to other terminal alkynes, with varying electronic demand (**Table 8**). Rates of reaction were dependent upon the identity of the aromatic unit, with electron rich substrates proceeding at a considerably slower rate than electron deficient substrates. A temperature of 55 °C was therefore chosen for all reactions to allow direct comparison of product distribution.

The transition metal-free, *anti*-Markovnikov addition of alkoxides to terminal alkynes was therefore achieved for a range of alkynes, including both electron rich and deficient analogues. For the more electron rich examples, higher reaction temperatures were required in order to achieve complete conversion within a reasonable timeframe (**Table 8**, **Entries 5**,**6** and **9**,**10**). No product was observed when using cyano-substituted phenylacetylene **127h**, with polymeric degradation products instead isolated. Interestingly, no product was observed for alkyl substituted alkyne **127j**, with complete recovery of the starting material instead observed (**Table 8**, **Entries 25** and **26**). The necessity for an aryl substituted alkyne is a common feature of reactions that proceed *via* an initial single electron transfer step,[140] and so may be indicative of a possible mechanism. In all cases, the addition of DMEDA led to a significant improvement in yield, of the order of 20% and sometimes higher.



127a-j ***E*-126a-j** ***Z*-126a-j** **131** **132**

Entry	R	#	Temp. (°C)	Additive	Yield 126 (%)	*Z*:*E*	Other products
1		**127a**	55	-	49	66:34	-
2			55	DMEDA	70	68:32	-
3			55	-	<5	95:5	95% **127b**
4			55	DMEDA	<5	95:5	95% **127b**
5		**127b**	100	-	23	80:20	16% **127b**, 5% **132**
6			100	DMEDA	47	80:20	7% **127b**, 7% **132**
7			55	-	13	90:10	36% **127c**
8			55	DMEDA	34	91:9	56% **127c**
9			75	-	50	88:12	7% **132**
10		**127c**	75	DMEDA	69	84:16	7% **132**
11[a]			75	DMEDA	15	90:10	44% **127c**
12[b]			75	DMEDA	0	-	100% **127c**
13		**127d**	55	-	51	80:20	-
14			55	DMEDA	66	80:20	-
15		**127e**	55	-	57	61:39	-
16			55	DMEDA	72	60:40	-
17		**127f**	55	-	42	54:46	22% **131**
18			55	DMEDA	51	52:48	21% **131**
19		**127g**	55	-	37	41:59	14% **131**
20			55	DMEDA	53	41:59	14% **131**
21		**127h**	55	-	0	-	-
22			55	DMEDA			
23		**127i**	55	-	31	30:70	15% **131**
24			55	DMEDA	31	30:70	14% **131**

25		**127j**	55	-	0	-	100% **127j**
26			55	DMEDA			

[a] Reaction conducted with NaOMe
[b] Reaction conducted with LiOMe

Table 8

Similarly to the synthesis of biaryls, the importance of the potassium cation is clearly demonstrated by the diminished or lack of reactivity observed for sodium and lithium analogues respectively (**Table 8**, **Entries 11** and **12**). The degree of separation of alkoxide and metal cation again seems crucial to the success of the reaction.

7.2.2. Mechanistic Determination

One of the most significant observations is the dependency of the *Z*:*E* ratio upon the identity of the aromatic group. A clear increase in the sterically disfavoured *Z*-isomer of **126** can be observed upon increasing the electron density, whereas the opposite selectivity is observed upon moving to more electron deficient aromatic alkynes. The dependence of the *Z*:*E* ratio upon electron demand can be best depicted by comparison with the σ value of the Hammett parameter.[173] A close correlation between electron donating ability and *Z*-selectivity can clearly be observed in **Figure 7**, allowing prediction of the *Z*:*E* ratio for a chosen aromatic alkyne, an extremely powerful tool.

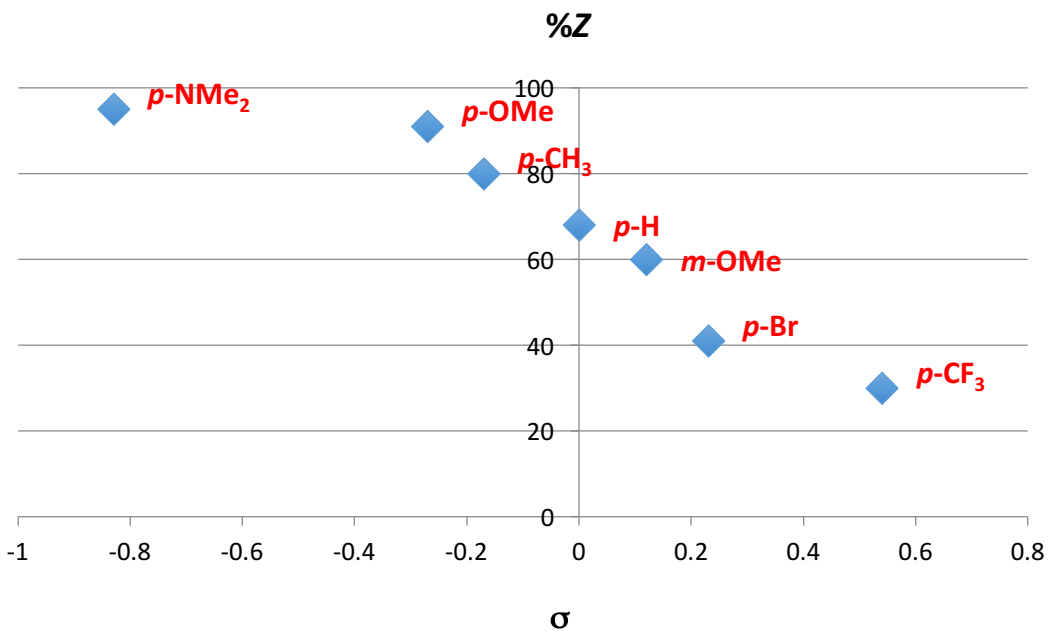
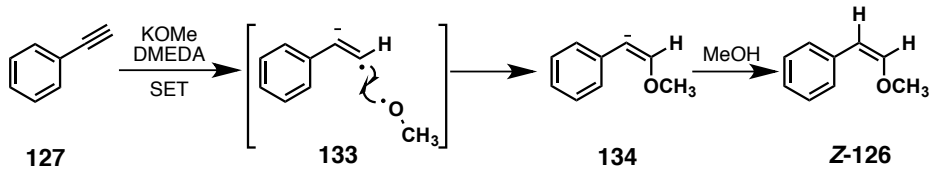


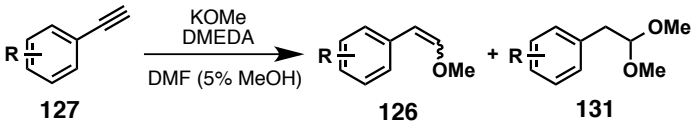
Figure 7

The *Z*-selectivity is redolent of that expected upon dissolving metal reductions of alkynes. Coupled with the increased efficiency of the reaction in the presence of a known single electron transfer promoter in DMEDA, and the critical nature of a potassium alkoxide over other Group 1 metals, a mechanism proceeding *via* an initial single electron transfer would seem feasible (**Scheme 103**).



Scheme 103

An initial single electron transfer would generate *trans*-disposed radical anion **133**. The failure of the reaction with alkyl substituted alkynes may be a result of insufficient stabilisation of this intermediate, or that initial electron transfer is assisted by the aromatic unit (**Table 8**, **Entries 25** and **26**). Rapid carbon-oxygen bond formation generates vinyl anion **134**, which may then be protonated by trace amounts of a proton source within the reaction medium to yield *Z*-enol ether **126**. In order to investigate the existence of a vinyl anion as a reaction intermediate, the general reaction of **Table 8** was repeated, with small amounts of a proton source included in the reaction medium. As such, the DMF used in reactions was spiked with 5% methanol (**Table 9**). Reactions were generally considerably more sluggish than in anhydrous media, as evidenced by the recovery of 55% **127c** after an extended reaction time of 30 h (**Table 9**, **Entry 1**). This could be the result of an impaired initial electron transfer reaction in the presence of small amounts of methanol. In all cases, a significant increase in *Z*-selectivity was observed, the most striking example being that of **127i** (**Table 9**, **Entry 3**). For this alkyne, a complete change in stereoselectivity was observed upon including a small amount of a proton source, selectively forming the *Z*-enol ether **126i** in an approximate 3:1 ratio. However, this result may also be expected if the reaction occurred *via* an ionic addition step (**Scheme 102**). The result can therefore not be used in isolation to suggest the presence of a single electron transfer mechanism, but must instead be considered within the context of further observations.



127 126 131

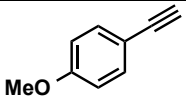
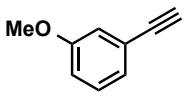
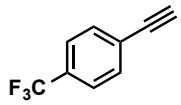
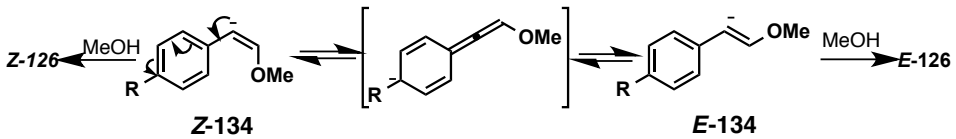
Entry	Alkyne	Temp (°C)	Yield 126 (%)	*Z*:*E*	Other
1		75	30	96:4	55% **127c**
2		55	65	81:19	28% **131**
3		55	30	74:26	32% **131**

Table 9

Attempts to elucidate the mechanism by selectively trapping the intermediate vinyl anion **134** with deuterated methanol were complicated by deuterium incorporation at the terminal alkyne position, a result of the facile deprotonation of terminal alkynes under the strongly basic conditions. The increased proportion of **131** formed in the presence of methanol can be explained by a simple ionic addition, not under the influence of an electron transfer reaction. Whilst the initial step in the reaction is attenuated in the presence of methanol, the formation of **131** is not.

The selective formation of the *Z*-isomers upon inclusion of small amounts of methanol strongly suggests the presence of vinyl anion **134**, hence indicating that *trans*-disposed radical anion **133** may initially be formed in the reaction. With the initially formed intermediate giving rise to the *Z*-isomer, it was therefore hypothesised that the *E*-isomer arose as a result of isomerisation of the *Z*-isomers under the strongly basic reaction conditions. To test this, a pure sample of *Z*-**126d** was isolated, and resubmitted to identical reaction conditions. Surprisingly, no isomerisation was observed, and *Z*-**126d** was recovered unchanged. Similarly, submitting a sample of pure *E*-**126d** to the same reaction conditions again resulted in no appreciable isomerisation, indicating an alternative mechanism must be in action.

In general, vinyl anions adopt a bent geometry, and have a significant barrier to inversion. As such, inversions are generally slow, and so access to appreciable amounts of the *E*-isomers *via* inversion of the *Z*-vinyl anions would seem unlikely. However, the fact that electron density may be delocalised over an aromatic ring may contribute to a lowering of this barrier, leading to the observed mix of *Z*- and *E*-products. In addition, Houk *et al*.[174] have demonstrated the influence of electron withdrawing groups upon the vinyl anion geometry and barrier to inversion. The inversion barrier was found to be significantly lowered upon substitution by cyano, methoxycarbonyl and formyl groups, allowing rapid interconversion to occur in solution, and low stereoselectivities to be observed. With this knowledge in hand, the formation of *E*-**126** can be seen to arise from the rapid inversion of *Z*-vinyl anions. The effects of electron withdrawing groups in lowering the barrier to inversion are well demonstrated by the increased proportion of *E*-product synthesised upon employing stronger electron withdrawing groups (**Table 10**).



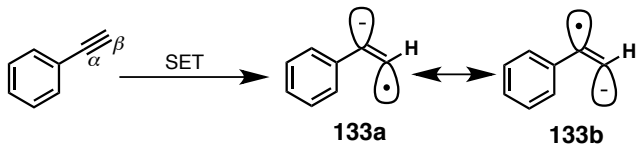
Z-134 *E*-134

Entry	R	σ	*E*-126 (%)
1	H	0	32
2	*m*-OMe	0.12	40
3	Br	0.23	59
4	CF_3	0.54	70

Table 10

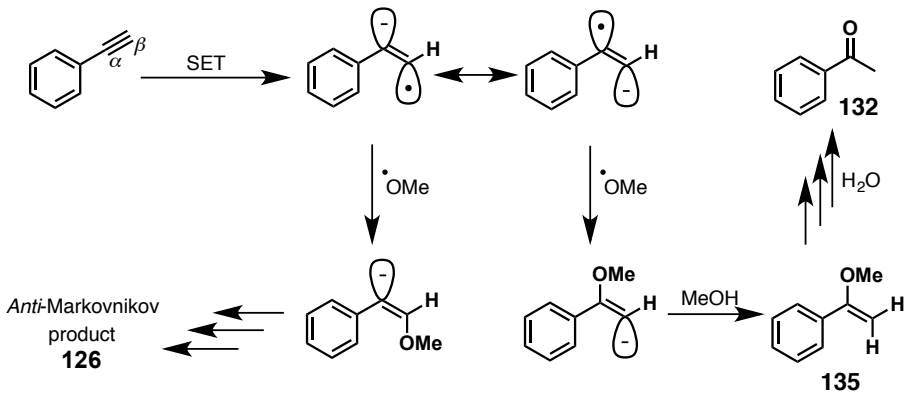
The proportion of *Z*-product formed is therefore dependent upon both the electronic character of the aromatic ring, and the lifetime of the intermediate vinyl anion. Under anhydrous reaction conditions, the initially formed *Z*-vinyl anion is long-lived enough to undergo inversion to give the sterically more favoured *E*-isomer. In the presence of a proton donor, however, rapid protonation of the vinyl anion prevents significant inversion occurring, leading to a significantly enhanced proportion of the *Z*-product, as observed.

The low yielding formation of ketone **132** observed for the highly electron rich terminal alkynes can also be accounted for by an underlying electron transfer mechanism (**Table 8**, **Entries 5**,**6** and **9**,**10**). Although initially resembling an alkyne hydrolysis reaction, the strongly basic reaction conditions make this pathway seem unlikely. Alternatively, upon single electron transfer to the π^* orbital of a terminal alkyne, the two radical anions **133a** and **133b** are equivalent (**Scheme 104**).



Scheme 104

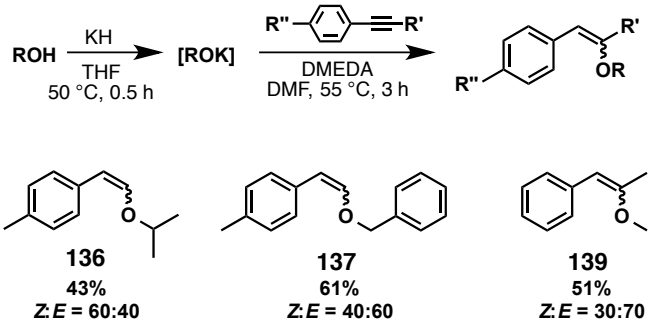
However, due to the delocalisation of negative charge over the aromatic ring, structure **133a** is dominant, with spin density concentrated on the β-carbon. As such, radical recombination generally occurs to give the *anti*-Markovnikov addition product. Increasing electron density within the aromatic ring, however, has a destabilising effect on the vinyl anion. As such, structure **133b** makes a contribution towards radical anion structure, and carbon-oxygen combination instead occurs at the α-carbon, leading to the Markovnikov addition product **135**. This enol ether is readily hydrolysed upon work-up of the crude reaction material, yielding the observed ketone **132** (**Scheme 105**).



Scheme 105

7.2.3. Further Substrates

The reaction was then extended to alternative alkoxides and internal alkynes to demonstrate the generality of the reaction. Potassium alkoxides could be prepared *in situ* by heating the parent alcohol with potassium hydride in THF, before removing the solvent under reduced pressure. Pleasingly, the enol ethers derived from isopropyl (**136**) and benzyl alcohol (**137**) could be formed in reasonable yields, with the same general trend for *E*:*Z* selectivity also observed (**Scheme 106**). The slightly eroded *Z*-selectivity arising from benzyl alcohol may have been a result of the influence of the benzyl unit, allowing relatively more rapid vinyl anion inversion compared to a simple alkyl chain.



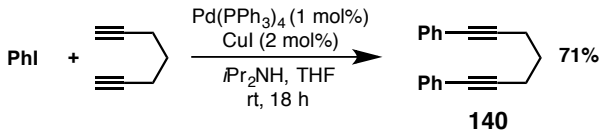
Scheme 106

For the reaction of internal alkyne **138** (R' = Me, R'' = H), the *Z*-selectivity was again depressed relative to terminal alkynes. However, the synthesis of **139** marks an improvement on the rhodium catalysed additions of alcohols to terminal alkynes published by Kakiuchi *et al*., for which no product was synthesised when using internal alkynes.[100]

In order to confirm the presence of radical intermediates in the reaction mechanism, the reaction with 4-methylphenylacetylene (**127d**) was repeated in the presence of TEMPO. Surprisingly, no attenuation of the reaction rate or yield were observed, indicating that a radical process may not be in operation. The result is similar to that observed by Wilden *et al*. in the synthesis of ynol ethers,[140] and Yorimitsu and Oshima *et al*.[175] in the hydrothiolation of alkynes in the presence of caesium carbonate. Similarly to the findings of this work, Yorimitsu and Oshima *et al.* noted high *Z*-selectivity, and diminished reactivity in the presence of the higher alkali metals,

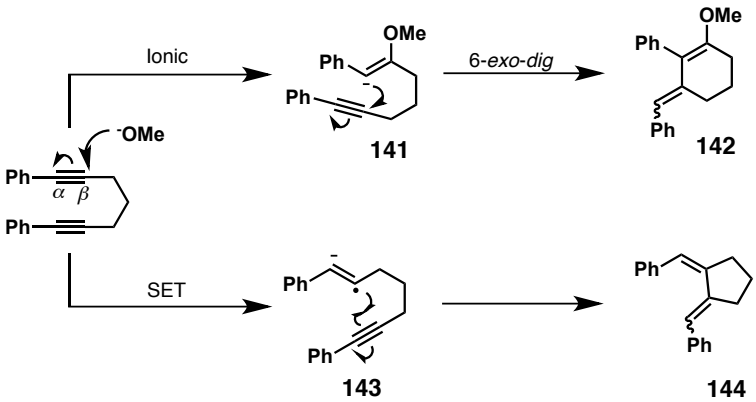
including sodium and lithium. However, conducting the reaction in the presence of the well known single electron acceptor 1,3-dinitrobenzene led to a decrease in yield from 66% to less than 10%. In combination with the observed *Z*-selectivity and improved yield in the presence of a secondary amine, this result increases confidence that an electron transfer pathway may play at least a competing role in the synthesis of enol ethers.

In order to increase the confidence in a radical mediated pathway, it was envisaged that substrates could be assembled so as to trap the initially formed radical anion. Extending the reaction to alternative alkynes had shown the general applicability to internal alkynes, with reactions proceeding with similar efficiencies and product distributions (**Scheme 106**). Exploiting this example, diyne **140** was synthesised *via* a Sonogashira reaction between 1,6-heptadiyne and iodobenzene (**Scheme 107**).[176]



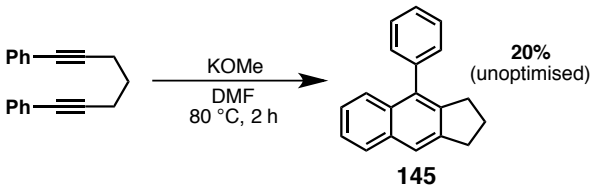
Scheme 107

If an ionic mechanism were in operation during the reaction of **140**, simple nucleophilic addition of methoxide might be expected to give addition products **141**, with inclusion of the methoxy group in the final product. Alternatively, *intra*molecular cyclisation *via* a favourable six-*exo*-*dig* would give rise to six-membered ring species such as **142** (**Scheme 108**). In contrast, by analogy to previous findings, a reaction mechanism that proceeds *via* an initial single electron transfer would be expected to give rise to radical anion **143**. With spin density located on the *β*-carbon, **143** would then be able to form five-membered ring species such as **144**, without inclusion of the methoxy group in the product.



Scheme 108

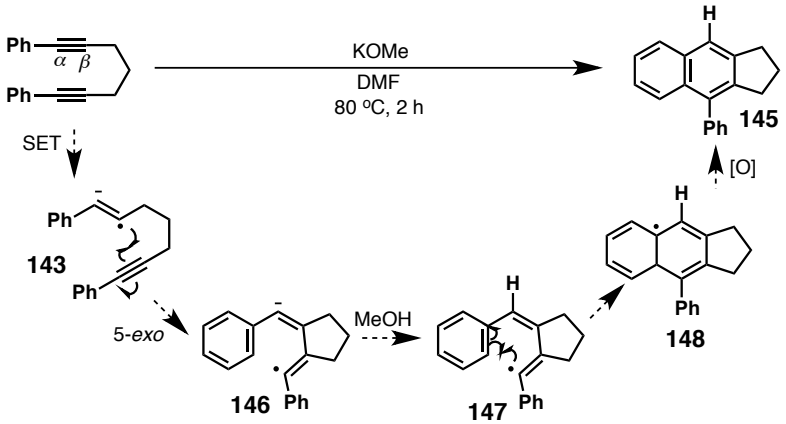
Subjecting **140** to the standard reaction conditions of **Table 8** resulted in a complex mixture of products, presumably due to uncontrolled radical processes. As control experiments had shown that the bulk effect of the reaction could be observed in the absence of added DMEDA (**Table 7**, **Entry 1**), the reaction was repeated in the absence of any additive (**Scheme 109**).



Scheme 109

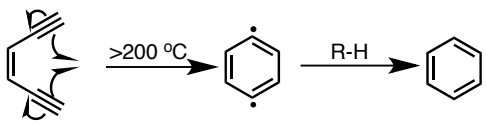
Pleasingly, the modified reaction conditions proved considerably milder, and **145** could be isolated in 20% yield, with the mass balance being accounted for by recovered starting material. Although an unexpected product, the synthesis of **145** is significant from a synthetic standpoint, as previous syntheses of **145** from **140** have generally required transition metal catalysis, usually employing Au(I).[177,178] Alternatively, previously published transition metal-free syntheses of **145** have required significantly harsher or lengthier reaction conditions to induce pericyclic processes (eg. 51–402 h,[177] 180–225 °C[179]). The synthesis of **145** in an unoptimised yield of 20% under relatively mild conditions therefore represents a significant improvement in access to functionalised naphthalenes, molecules that are important building blocks in synthesis.[180]

Although not the initially expected product, **145** strongly suggests that a radical mediated process is in operation. Initial single electron transfer from the alkoxide/secondary amine mixture yields *trans*-disposed radical anion **143**. With spin density located on the *β*-carbon, 5-*exo*-cyclisation then occurs as postulated, to yield radical anion **146**. Quenching of the reaction at this point would yield the expected 5-membered cyclisation product **144**. However, radical anion **146** may also be quenched by traces of methanol or moisture within the reaction mixture to give vinyl radical **147**, which is appropriately aligned to undergo addition to an aryl group. Radical **148** would be expected to undergo rapid rearomatisation, yielding the observed naphthalene derivative **145** (**Scheme 110**). Alternatively, **144** could undergo an electrocyclic cyclisation and subsequent oxidation to form **145**.



Scheme 110

Although the reaction product resembles that which might be expected from a typical Bergman cyclisation (**Scheme 111**),[181] such a mechanism seems unlikely in this case. The conditions are considerably milder than those typically employed in the synthesis of **145** *via* pericyclic processes, or in related Bergman-type cyclisations. In addition, the presence of potassium methoxide was found to be crucial to the success of the reaction, with a negligible amount of **145** observed upon heating diyne **140** in DMF alone. Taking into account the single electron transfer abilities of alkoxides, the initial formation of a radical anion seems likely.

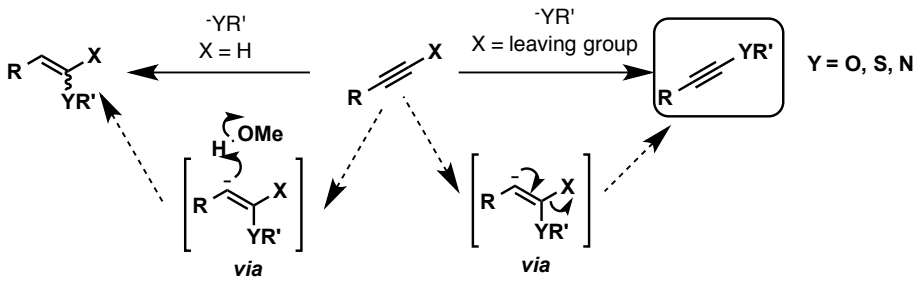


Scheme 111

The combination of a potassium alkoxide and a secondary amine has previously been shown to behave as a potent source of reducing power. In the current work, experiments have highlighted the possibility that the *anti*-Markovnikov, transition metal-free synthesis of enol ethers under relatively mild conditions could proceed *via* an electron transfer mechanism. Whilst the observed *Z*-selectivity of enol ethers could be accounted for by either an ionic or electron transfer mechanism (**Scheme 102**), the high *Z*-selectivity in combination with additional evidence suggests an electron transfer mechanism to be possible. For instance, the requirement for an aryl substituted alkyne, an increase in yield in the presence of a secondary amine, a significant decrease in yield in the presence of a single electron transfer inhibitor, and the products observed in the reaction of radical probe **140** together highlight the possibility that a single electron transfer mediated mechanism is feasible. A single electron transfer mechanism can therefore account for the products observed in a reaction that is generally believed to proceed *via* ionic intermediates. With an enhanced understanding of the underlying mode of reactivity of this potent combination of reagents, the same principles can be extended to the transition metal-free synthesis of other molecules which would be otherwise difficult to make.

8. Synthesis of Alkynyl Sulfides

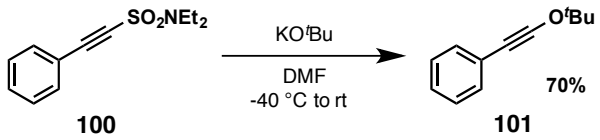
With evidence to suggest the possibility of a radical anion mediated pathway in the reactions of terminal alkynes with potassium alkoxides, the substrate focus changed to internal alkynes. Specifically, alkynes were chosen that were substituted with an appropriate leaving group that, upon formation of an intermediate vinyl anion, could undergo elimination and yield substituted alkynes (**Scheme 112**). Such an approach would give ready access to heteroatom-substituted alkynes such as ynol ethers, alkynyl sulfides and ynamines, molecules that generally require laborious syntheses.



Scheme 112

8.1. Initial Observations and Optimisation

Previous work within the group had identified alkynyl sulfonamide **100** as a suitable precursor to ynol ethers **101**, allowing rapid synthesis of a broad range of alkynyl ethers (**Scheme 113**).[140]

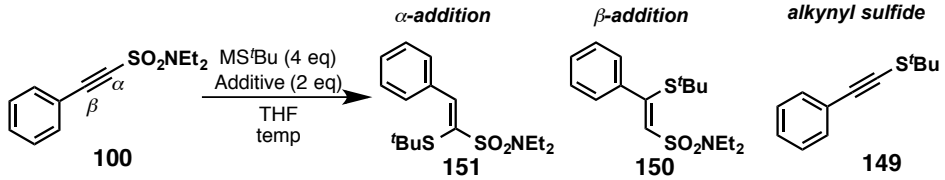


Scheme 113

The increased rate of DMF decomposition to carbon monoxide and *N*,*N*-dimethylamine in the presence of a strong base such as potassium *tert*-butoxide[168] instantly allows parallels to be drawn with the findings of Kwong and Lei *et al*.,[56] and previous work within the group. With past work in the group confirming that the combination of an alkoxide base and secondary amine additive is a potent source of reducing power, the replacement of DMF with a solvent that is easier to remove from

reaction mixtures such as THF, and the controlled addition of a secondary amine allowed access to ynol ethers **101** in high yields.[182]

With approaches to alkynyl sulfides generally requiring the deprotonation of a terminal alkyne, an attempt was made at their synthesis *via* an *sp*-displacement reaction. The secondary amine *N*,*N*-dimethylamine was included in reactions of potassium thiolates with alkynyl sulfonamide **100**. With a boiling point of 7 °C, *N*,*N*-dimethylamine is commercially available as a 2.0 M solution in THF, and may be readily removed during reaction work-up. Potassium thiolates could readily be formed *in situ* by heating four equivalents of the parent thiol with an equimolar amount of potassium hydride in THF at 50 °C for 20 minutes. An initial reaction between potassium *tert*-butylthiolate and **100**, in anhydrous THF taken from a SureSeal^{TM} bottle that had been open for over two weeks, gave a trace of alkynyl sulfide **149**, *β*-addition product **150**, and a considerable amount of *α*-addition product **151** (**Table 11**, **Entry 1**).

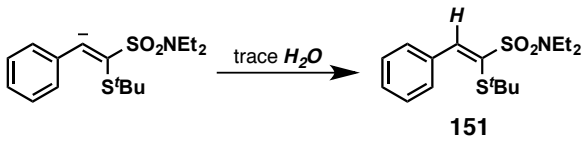


Entry	M^+	Additive	Temp (°C)	151 (%)	150 (%)	149 yield (%)
1[a]	K^+	$HNMe_2$	rt	55	17	Trace
2[a]	Na^+	$HNMe_2$	rt	51	17	Trace
3[a]	K^+	$HNMe_2$	–40	82	3	Trace
4[b]	K^+	$HNMe_2$	–40	39	Trace	38
5[c]	**K^+**	**$HNMe_2$**	**–40**	**7**	**Trace**	**64**
6[d]	K^+	$HNMe_2$	–40	10	Trace	24
7	Na^+	$HNMe_2$	–40	35	17	20
8	K^+	-	–40	30	15	48
9[e]	K^+	$HNMe_2$	–40	45	17	6

[a] THF was from an anhydrous bottle that had been open for several weeks, sulfonamide predissolved in 0.5 mL THF
[b] THF was from an anhydrous bottle that had been open for several weeks, sulfonamide NOT predissolved
[c] THF was fresh from solvent stills, sulfonamide NOT predissolved
[d] 2.0 equivalents of thiol used, 48% sulfonamide **100** recovered
[e] Vessel open to the atmosphere

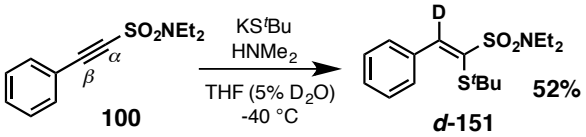
Table 11

Initial optimisation experiments made use of standard grade THF, taken from a bottle that had been open for several weeks. In the presence of this THF, the metal counterion had little effect on product distribution (**Table 11**, **Entries 1** and **2**), which instead appeared to be driven by the presence of a proton source. Given the hydroscopic nature of THF, it was hypothesised that water present in the reaction might have caused the large amount of α-addition product **151** *via* trapping of a vinyl anion, hence preventing further reactivity (**Scheme 114**).



Scheme 114

By not premixing the alkynyl sulfonamide in 0.5 mL THF prior to addition to the reaction mixture, the yield of **149** increased from a trace to 38% (**Table 11**, **Entry 4**), probably a result of reduced water content within the reaction. Changing from THF taken from a SureSeal^{TM} bottle that had been open for several weeks to THF taken directly from solvent stills significantly improved the yield of **149**, increasing to 64% (**Table 11**, **Entry 5**),[182] thereby highlighting the role played by water in suppressing alkynyl sulfide formation. In order to determine the origin of the vinylic proton in the α-addition product **151**, the reaction was conducted in a THF solution spiked with 5% D_2O. Pleasingly, over 85% deuterium incorporation was observed at the vinyl position only, indicating that the α-addition product arises from the quenching of a carbanion, and not hydrogen abstraction by a radical species (**Scheme 115**). Initial attempts to trap the vinyl anion with alternative electrophiles (eg. *N*-chlorosuccinimide) were unsuccessful.



Scheme 115

Cooling the reaction was found to significantly decrease the amount of β-addition product **150** isolated (**Table 11**, **Entry 3**). In the presence of a reduced number of

thiolate equivalents, incomplete conversion of **100** was observed (**Table 11**, **Entry 6**). Four equivalents of thiolate were therefore employed for all further reactions.

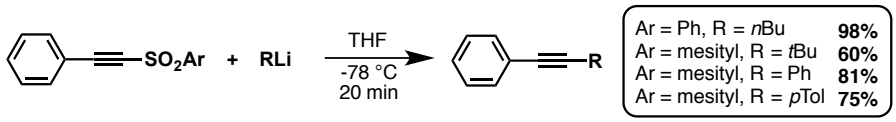
Similarly to additions of alkoxides to terminal alkynes, the presence of a secondary amine drastically affects the product ratio. In contrast to the previously reported synthesis of ynol ethers, however, the amine is not crucial to reactivity. Repeating the reaction without added amine gave a significantly more complex mixture of products, and substantially lower yield of **149** (**Table 11**, **Entry 8**). Whilst the exact role played by secondary amines remains elusive, they clearly play a role in stabilising an intermediate species.

Conducting the reaction with sodium *tert*-butylthiolate again led to the alkynyl sulfide **149**, though in a lower yield of 20%. This result was at first surprising given the sharp cut off in reactivity seen for ynol ether synthesis, in which no reaction was observed with sodium alkoxides (**Scheme 113**).[140] However, the increased reactivity of sodium salts would be expected when considering the increased ability of thiolate anions to partake in single electron transfer reactions compared to alkoxides. As such, the second equilibrium of **Scheme 84** would move to the right relative to that expected of alkoxides, increasing the concentration of 'loosely bound' electrons available to partake in electron transfer reactions. The reactivity cut off is less well defined than for alkoxides, though the same general trend is observed. Indeed, an increase in β-addition upon employing sodium thiolate is indicative of a greater ionic contribution to the reaction, resulting in Michael addition. Exposure of the reaction mixture to the atmosphere significantly retarded the reaction (**Table 11**, **Entry 9**).

8.2. Displacement at *sp*-Centres – A Comparison

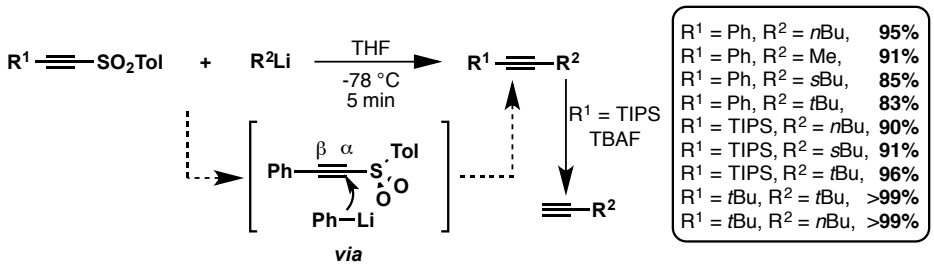
The synthesis of alkyl sulfides therefore constitutes a displacement at an *sp*-centre. Such transformations are unusual, especially with heteroatomic nucleophiles. Sulfones and sulfonamides have commonly been employed as appropriate leaving groups. Truce and Smorada[183] disclosed the first use of carbon nucleophiles in the reaction with acetylinic sulfones in 1979. Treatment of acetylinic sulfones with an equimolar amount of an organolithium reagent in THF at –78 °C gave facile access to

acetylenes, with only the product arising from *anti*-Michael addition observed (**Scheme 116**).



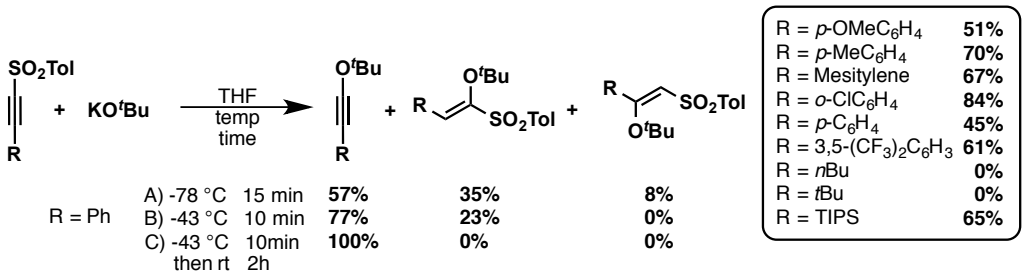
Scheme 116

García Ruano *et al.*[184,185] considerably expanded the work of Truce *et al.*, applying organolithium derivatives to both alkyl and aryl substituted acetylinic sulfones, with products obtained rapidly and in excellent yields (**Scheme 117**). Similarly to Truce *et al.*, the authors invoke an association between sulfonyl oxygen atoms and lithium reagent, followed by an ionic addition-elimination mechanism at the α-carbon in order to account for the *anti*-Michael selectivity. Indeed, computational studies confirmed the lowering of the activation barrier to *anti*-Michael addition upon complexation.



Scheme 117

Subsequently, García Ruano *et al.*[186] extended their alkynylation reaction to the synthesis of ynol ethers (**Scheme 118**). Again making use of sulfones, treatment with potassium *tert*-butoxide allowed access to a wide range of aromatic- or triisopropylsilyl-substituted *tert*-butyl ynol ethers. Interestingly, the reaction works simply with THF as solvent, contrary to the findings of Wilden *et al*.,[140] presumably a result of the greater electron withdrawing capacity of the sulfone group compared to that of the sulfonamide unit of **100**.



Scheme 118

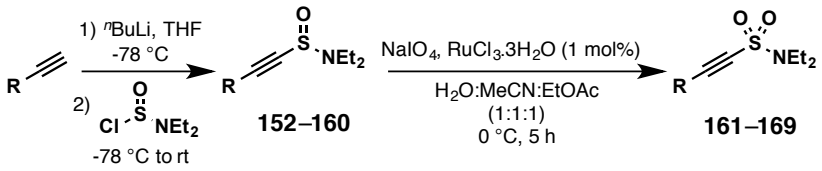
High yields of ynol ether required a relatively long reaction time of two hours (*c.f.* 5 minutes, Wilden *et al.*[140]). The authors again invoke a complexation between potassium *tert*-butoxide and sulfonyl oxygen atoms to account for the observed regioselectivity.

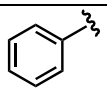
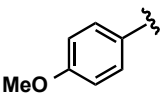
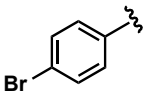
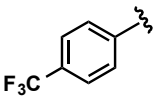
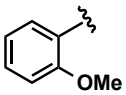
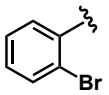
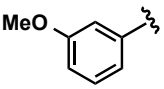
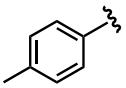
The synthesis of alkynyl sulfides from alkynyl sulfonamides therefore represents a significant contribution towards the synthesis of heteroatom-substituted alkynes *via* a direct displacement at an *sp*-centre.

8.3. Reaction Scope

8.3.1. Sulfonamide Substrate Synthesis

With optimised conditions developed for the synthesis of alkynyl sulfide **149** from alkynyl sulfonamide **100**, it was important to examine the scope and limitations of the reaction. A range of aryl and alkyl substituted alkynyl sulfonamides **161**–**169** could rapidly be synthesised in a two-step process from commercially available acetylenes (**Table 12**).[140] Initially, terminal acetylenes were deprotonated using ^{n}BuLi, followed by addition of a sulfinamide source, $SOClNEt_2$. The highly reactive $SOClNEt_2$ was prepared according to the protocol of Baudin *et al.*,[187] *via* the dropwise addition of two equivalents of dimethylamine to thionyl chloride in anhydrous ether. The sulfurous chloride was stored under argon at –20 °C when not in use, with rapid evolution of HCl occurring upon exposure to air. Oxidation of sulfinamides **152**–**160** by sodium *meta*-periodate and catalytic ruthenium(III) chloride proceeded smoothly at 0 °C to yield sulfonamides **161**–**169**, with the mass balance accounted for by over oxidation products and recovered starting material.



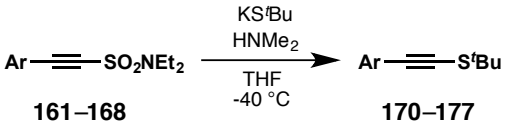
Entry	R	Sulfinamide	Yield (%)	Sulfonamide	Yield (%)
1		**152**	51	**161**	54
2		**153**	72	**162**	42
3[a]		**154**	86	**163**	31
4		**155**	45	**164**	43
5		**156**	91	**165**	37
6		**157**	79	**166**	53
7		**158**	65	**167**	34
8		**159**	79	**168**	45
9		**160**	92	**169**	45

[a]Deprotonated with KHMDS

Table 12

8.3.2. Alkynyl Sulfide Scope

Though yields obtained from the oxidation step were somewhat disappointing, ready access to a range of alkynyl sulfonamides was established, and the reaction with potassium thiolates and *N*,*N*-dimethylamine could be investigated. Pleasingly, displacement of the sulfonamide unit was observed for all aromatic-substituted alkynyl sulfonamides **161–168** (**Table 13**).



161–168 170–177

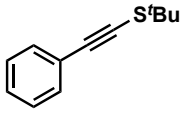
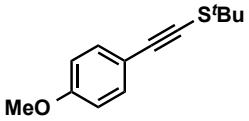
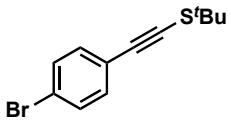
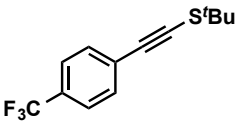
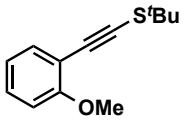
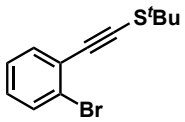
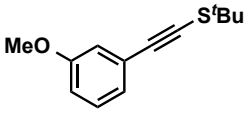
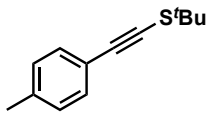
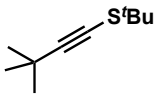
Entry	Sulfonamide	Alkynyl Sulfide		Yield (%)
1	**161**		**170**	64
2	**162**		**171**	32
3	**163**		**172**	59
4	**164**		**173**	63
5	**165**		**174**	51
6	**166**		**175**	72
7	**167**		**176**	49
8	**168**		**177**	73
9	**169**		**178**	0

Table 13

The reaction is tolerant of both electron donating and withdrawing groups, proceeding with similar efficiencies for both. Significantly, none of the expected alkynyl sulfide was observed for the *tert*-butyl substituted alkynyl sulfonamide **169** (**Table 13**, **Entry 9**), with the Michael addition product instead observed. A mechanistic reasoning for

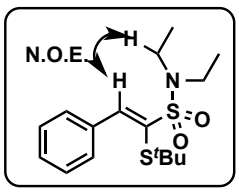
this will be presented later. Nevertheless, the reaction with aromatic substituted alkynyl sulfonamides represents a rapid and tolerant approach to alkynyl sulfides proceeding *via* an unusual displacement at an *sp*-centre.

8.4. Mechanistic Understanding

With previous work in the group determining that alkoxides have inherent electron transfer abilities, it was hypothesised that potassium thiolates may behave in a similar manner. Indeed, Ashby *et al*. have noted a general trend of single electron transfer ability, increasing from alkoxides to thiolates.[16] In addition, Ashby and co-workers have provided EPR evidence supporting an electron transfer mechanism in the reactions of lithium thiolates with alkyl halides and aromatic ketones.[188] Considering work with terminal alkynes also, a possible radical mediated reaction pathway was therefore investigated.

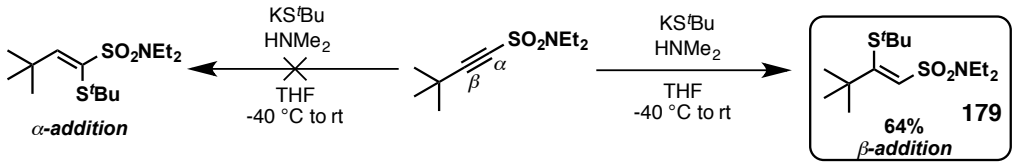
8.4.1. Radical Mediated Pathway

Whilst the work of Garcia Ruano *et al*. suggests that an ionic mechanism is in operation for similar systems, several observations have made a radical mediated process seem more likely. For instance, the α- and β-addition products **151** and **150** are formed as single geometrical isomers. The *Z*-stereochemistry with respect to the phenyl ring and sulfide unit was confirmed by NOESY experiments (**Scheme 119**), and is indicative of the mechanism, being analogous to the expected stereochemistry obtained *via* dissolving metal reductions of alkynes. In addition, the *Z*-product has identical stereochemistry to that isolated during ynol ether synthesis from **100**, a process shown *via* EPR spectroscopy to be radical mediated.[189]



Scheme 119

None of the expected alkynyl sulfide was observed in the reaction of alkyl substituted alkynyl sulfonamide **169** (**Table 13**, **Entry 9**). Instead, the Michael addition product **179** was formed exclusively. Clearly therefore, an aromatic unit is required to direct addition towards the α-position. Aromatic units may help in the stabilisation of the *trans*-disposed intermediates. Such a requirement for aromatic substituted substrates is common in mechanisms that proceed *via* a single electron transfer step. Unable to provide this increased stabilisation, addition of nucleophiles to the α-position of alkyl substituted alkynyl sulfonamides is unfavoured, with Michael addition instead dominating (**Scheme 120**).



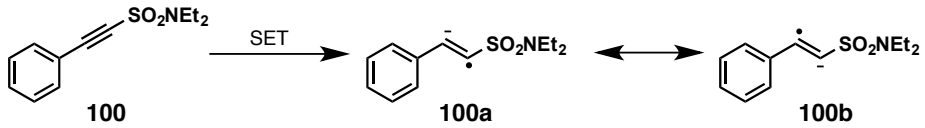
Scheme 120

It therefore seems likely that the reaction proceeds *via* radical intermediates. Such a mechanism would account for the low yield of alkynyl sulfide, and high yield of α-addition product isolated from *para*-methoxy substituted alkynyl sulfonamide **162**. Delocalisation of electron density from the methoxy group would increase the reactivity of a vinyl anion towards protonation, which may be rationalised as a pseudo-alpha effect.

8.4.2. Mechanism

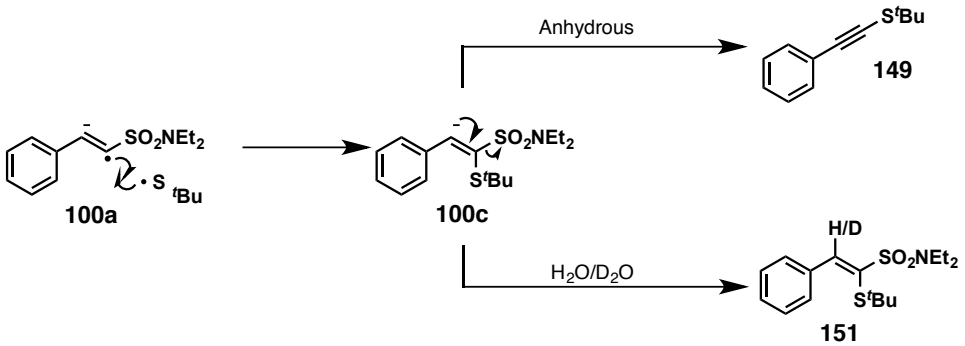
As a known single electron donor, a possible mechanism could involve electron transfer from the thiolate-secondary amine mixture, to the alkynyl sulfonamide **100**, generating radical anion **100a** (**Scheme 121**). Whilst the exact role played by the amine in radical generation is unknown, a role in assisting sulfur radical stabilisation can be inferred from the more complex mixture obtained in its absence. The presence of an aromatic unit attached to the triple bond of **100** is crucial to the stabilisation of the resultant radical anion **100a**, hence the observed suppression of radical reactivity with **169**. Radical anion **100a** is formed as a single, *trans*-disposed isomer. The two structures **100a** and **100b** are equivalent, though computational modelling has shown that, in the most stable conformation, charge density is centred on the carbon atom

adjacent to the aromatic ring, whereas spin density is focussed on the alkenyl carbon atom adjacent to the sulfonamide unit. The reason for this selectivity is unclear, though similarly to terminal alkynes, may be driven by delocalisation of the anion around the aromatic ring.



Scheme 121

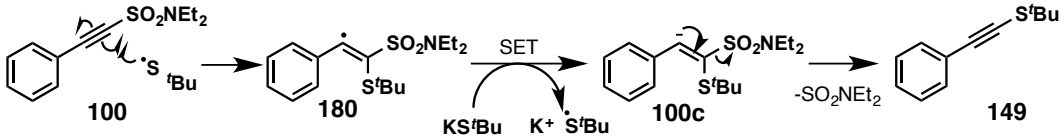
Combination of radical anion **100a** with an electrophilic sulfur-centred radical generates vinyl anion species **100c**, which may eliminate SO_2NEt_2 and form an alkynyl sulfide (**149**) under anhydrous conditions, or alternatively form the α-addition product **151** in the presence of a proton source (**Scheme 122**). The presence of the vinyl anion has been confirmed previously by deuterium incorporation in the presence of D_2O.



Scheme 122

In the possible mechanism outlined in **Scheme 122**, the carbon-sulfur bond forming process occurs between a radical anion and a sulfur-centred radical species. The termination reaction between two free radical species would be expected to be rare, due to the inherently low concentrations of two transient species. However, the radical anion imparts a greater degree of stability to the intermediates, increasing the likelihood of such combination reactions. In addition, a radical "cage" may be invoked to account for the reaction success. Following single electron transfer, the sulfur centred radical does not diffuse from the solvent cage and does not behave as a 'free' radical, thereby increasing the inherent probability of combination.

An alternative possible mechanism may envisage the direct addition of thiol radicals to the alkyne of **100**, affording an intermediate vinyl radical **180**. A subsequent electron transfer from a further molecule of potassium thiolate would generate the same vinyl anion intermediate **100c** as previously (**Scheme 123**), with elimination yielding the expected alkynyl sulfide **149**. However, the necessity of substitution by an aromatic unit and the strict stereochemistry observed for the α- and β-addition products make an initial electron transfer reaction seem more likely.



Scheme 123

In order to confirm the presence of radical intermediates, the reaction was repeated in the presence of established radical inhibitors. Pleasingly, conducting the reaction in the presence of one equivalent of galvinoxyl inhibited the reaction, with no alkynyl sulfide observed.

Aware of the ease with which sulfur-centred radicals may be generated upon exposure of thiols to UV light,[190] control reactions were carried out in the dark. Satisfyingly, no suppression of alkynyl sulfide yield was observed, eliminating the possibility of UV light assisting in radical generation.

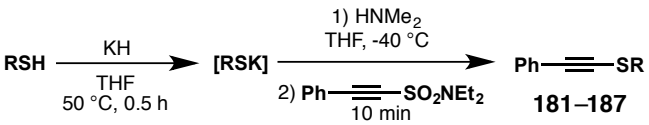
8.5. Further Substrate Elaboration

With a firm understanding of the reaction mechanism, alternative thiols could be employed to make a range of *S*-substituted alkynyl sulfides. Potassium thiolates could be formed *in situ* from the parent thiol and potassium hydride, and used as previously in a one-pot procedure (**Table 14**).

The reaction worked well for the synthesis of primary alkynyl sulfides (**Table 14**, **Entries 1**–**4**), with products obtained in good yields. However, the use of thiophenol led to none of the expected alkynyl sulfide, with the α- and β-addition products instead obtained in 3% and 67% yields respectively (**Table 14**, **Entry 5**). The opposite

selectivity observed may be accounted for by the reduced electrophilicity of the thiophenol radical compared to alkyl variants.

Secondary thiols proved troublesome, with the alkynyl sulfide isolated in low yields, and the majority of the reaction mixture composed of the α-addition product (**Table 14**, **Entries 5** and **6**). The reason for the failure of the reaction with secondary thiolate ions remains unclear, though the high proportion of α- addition product suggests that it may be due to adventitious water, present in the parent thiol, that traps an intermediate vinyl anion as the α-addition product. Hence, no elimination to form alkynyl sulfides can occur.



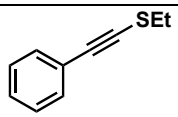
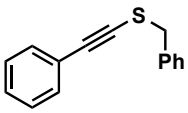
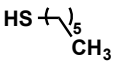
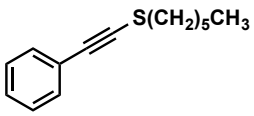
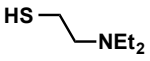
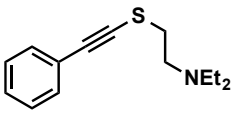
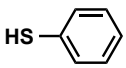
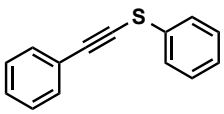
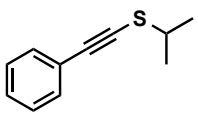
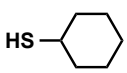
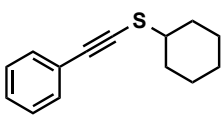
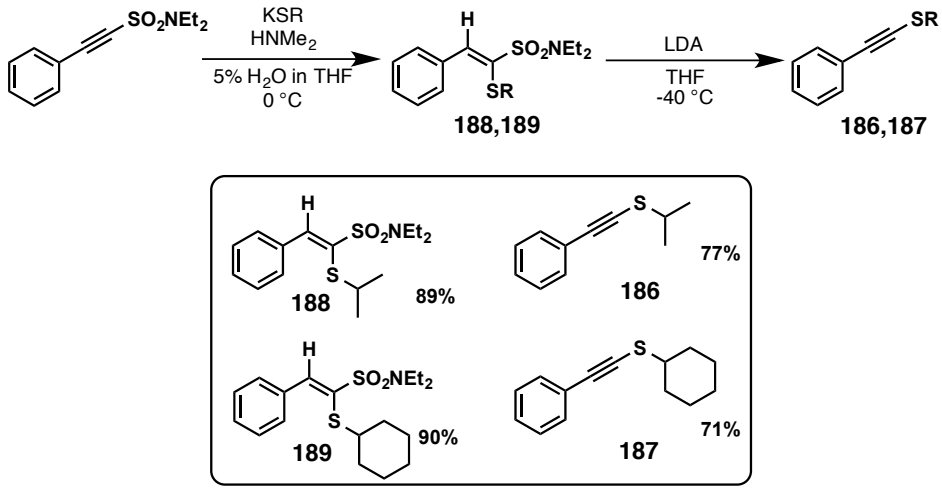
Entry	RSH	Alkynyl Sulfide		Yield (%)
1	HSEt		**181**	59
2			**182**	24
3			**183**	62
4			**184**	56
5			**185**	-
6			**186**	16
7			**187**	<5

Table 14

The intolerance of the method towards trace amounts of water could, however, be exploited *via* a two-step reaction procedure. Deliberate spiking of the reaction mixture with small amounts of a proton source is known to yield the α-addition products **188** and **189** as a single geometrical isomer (**Scheme 124**). Therefore, conducting the reaction in THF that had been spiked with 5% H_2O yielded exclusively the α-addition product. Subsequently, the strong *ortho*-directing properties of the sulfonamide group[191] resulted in smooth deprotonation upon treatment with LDA, with elimination of lithium *N*,*N*-diethylamidosulfite occurring as in previous mechanisms. The result is significant not only because alkynyl sulfides **186** and **187** may be synthesised from troublesome secondary thiols, but because a compound that was thought to be an undesirable side-product, the α-addition product, could in fact be used to synthesise the desired product, increasing atom economy.



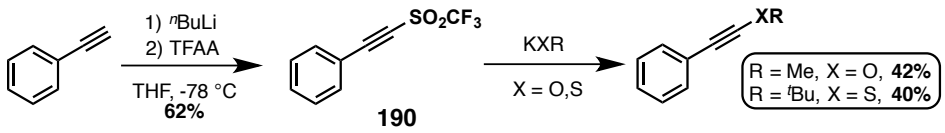
Scheme 124

Similarly to the synthesis of biaryls, the reaction between alkynyl sulfonamide **100** and potassium *tert*-butylthiolate was therefore found to also proceed in the absence of a secondary amine additive. However, the presence of *N*,*N*-dimethylamine resulted in a significant increase in the yield of alkynyl sulfides synthesised (**Table 11**, **Entry 8**). In addition, conducting reactions in the absence of a secondary amine led to a significantly more complex reaction mixture, with several unidentified trace products contaminating the alkynyl sulfide product. Secondary amines in general, and specifically *N*,*N*-dimethylamine in this work, therefore play an as yet unidentified role

in radical generation, presumably *via* stabilisation of an initially formed sulfur-centred radical.

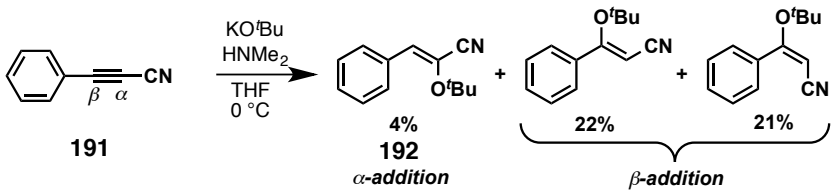
8.6. Alternative Alkynylating Substrates

Clearly, the use of alkynyl sulfonamides, whilst allowing facile access to alkynyl sulfides, does not represent an atom economic approach, with their synthesis requiring two synthetic steps and a transition metal catalysed oxidation. In light of this, alternative substrates were investigated as suitable alternatives. Deprotonation of terminal alkynes with ^{n}BuLi and treatment with triflic anhydride gave rapid access to alkynyl sulfone **190**. However, despite also giving rise to ynol ethers and alkynyl sulfides upon treatment with potassium alkoxides and sulfur analogues respectively, yields were significantly lower than those achieved with alkynyl sulfonamide **100**, possibly a result of a highly reactive trifluoromethyl species in the reaction mixture upon sulfone elimination (**Scheme 125**).



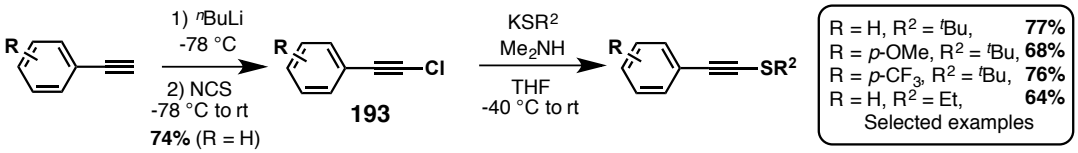
Scheme 125

Extending the scope beyond sulfones, 3-phenyl-2-propynenitrile (**191**) was employed as a potential route to heteroatom substituted alkynes. Upon treatment with potassium *tert*-butoxide and dimethylamine in THF, the α-addition product **192** was isolated in an unoptimised yield of 4%, with the remaining mass balance made up of β-addition products (**Scheme 126**). Despite the low yield, the isolation of any α-addition product is significant, indicating that *anti*-Michael addition can be achieved using substrates other than sulfones and sulfonamides. However, the general tendency towards Michael addition prevented further exploration using the substrate.



Scheme 126

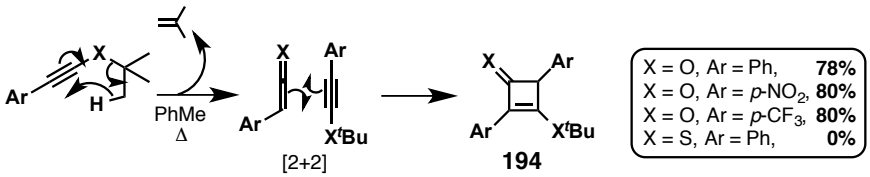
Recently, work in the group has shown that alkynyl sulfides can be readily synthesised from chloroacetylenes (**Scheme 127**).[192] Substrate synthesis is rapid, requiring deprotonation of a terminal alkyne, then treatment with cheap and readily available *N*-halosuccinimides to yield chloroacetylene **193**. Exposure to potassium thiolate salts and *N*,*N*-dimethylamine in THF yields alkynyl sulfides in good to excellent yields, with a wide scope of aromatic functionality tolerated. A mechanism similar to that for alkynyl sulfide synthesis *via* alkynyl sulfonamide **100** has been proposed.



Scheme 127

8.7. Reactions of Alkynyl Sulfides and Ynol Ethers

Despite the inherent polarisation of the alkyne unit, alkynyl sulfides proved to be remarkably unreactive. For instance, mild heating of *tert*-butyl ynol ethers is known to extrude *iso*-butene and generate ketenes, which can either be trapped by nucleophiles,[193] or undergo an *intra*molecular [2+2] cycloaddition with a further molecule of ynol ether to yield cyclobutane rings **194** (**Scheme 128**).[140] However, heating alkynyl sulfide **149**, even to 150 °C in toluene, failed to yield any products arising from thioketene formation, with complete recovery of starting material instead observed.



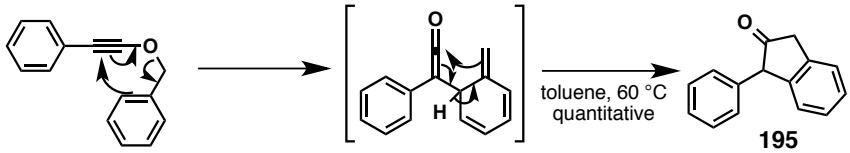
Scheme 128

As such, focus was switched to ynol ethers, with the hope of exploiting the increased reactivity of the triple bond in synthesis. Although ynol ethers have been utilised previously in synthesis, substrate scopes are often severely restricted, owing to the limited number of methods available for their synthesis. Literature syntheses generally rely upon an elimination reaction of alkenyl ethers. To this end, trichloroethylene has

been widely utilised in ynol ether synthesis, with Greene *et al*.[125] disclosing the first general approach (**Scheme 70**). However, with a rapid and high yielding approach to heteroatom substituted alkynes at hand, further research into the behaviour of ynol ethers could be conducted.

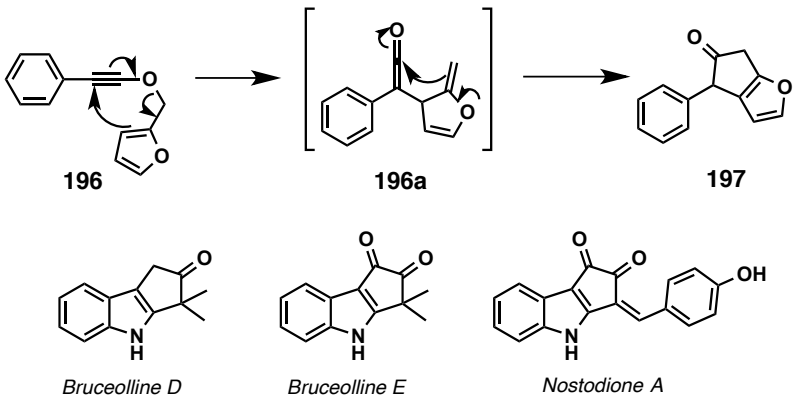
8.7.1. Furan Reactions and Rearrangements

With an alternative synthesis of heteroatom substituted alkynes *via* alkynyl sulfonamides in hand, rapid access to a broad range of substrates could be achieved, and their reactivity exploited. In their synthesis of phenylethynyl benzyl ether, Minehan *et al*. noticed that the ynol ether underwent a [3,3] rearrangement followed by *intra*molecular ketene trapping to yield indanone **195** (**Scheme 129**).[194]



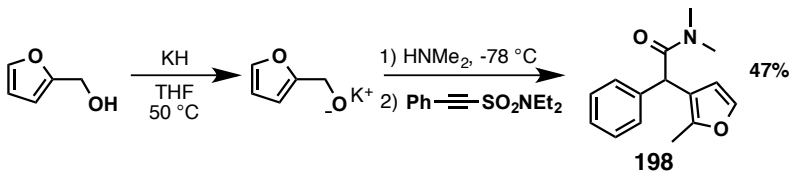
Scheme 129

Taking inspiration from this reaction, attempts were made to synthesise the novel furan analogue **197**. Such a molecule closely resembles the core structure of the underexplored *Bruceollines*[195], and the marine bacteria *Nostodione A*,[196] which is known to have antifungal and antibiotic properties.[197] Rapid access to the core scaffolds of these natural products therefore appeared possible (**Scheme 130**). It was hypothesised that ynol ether **196** would undergo a [3,3] cycloaddition to yield ketene **196a**, which could be trapped *intra*molecularly by the enol ether moiety to yield **197**.



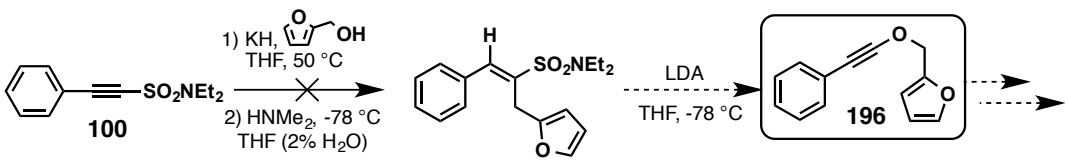
Scheme 130

The potassium salt of furfuryl alcohol could be readily prepared as previously. Reaction with alkynyl sulfonamide **100** in the presence of *N*,*N*-dimethylamine at –78 °C instantly formed a dark brown reaction mixture, with complete starting material consumption observed *via* TLC. However, upon purification *via* column chromatography, the expected product was not isolated. Instead, **198**, formed *via* the addition of *N*,*N*-dimethylamine to the ketene of intermediate **196a** was observed in 47% yield (**Scheme 131**). The product indicates that initial formation of ynol ether **196**, and [3,3] cycloaddition were successful at –78 °C, though the ketene is preferentially trapped by the amine, rather than undergoing *intra*molecular cyclisation.



Scheme 131

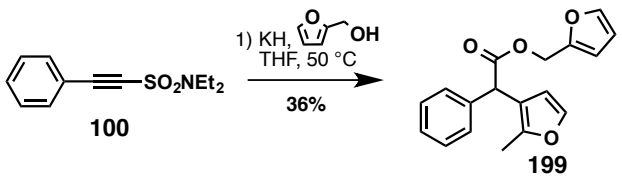
With the presence of a secondary amine crucial to the synthesis of ynol ethers,[182] alternative approaches to the core structure were attempted. With the knowledge that spiking the reaction mixture with a small amount of a proton source led exclusively to the α-addition product, a THF solution containing 2% v/v water was utilised. Isolation of the α-addition product would be followed by elimination of the sulfonamide unit in the presence of LDA (**Scheme 132**), allowing access to the ynol ether **196**. Ketene formation could then be achieved in the absence of a secondary amine. However, the presence of water was found to prevent any addition of the alcohol to **100**, with almost complete recovery of the starting material observed.



Scheme 132

As an alternative, the amine was excluded from the reaction. The potassium salt of furfuryl alcohol was formed as previously, and then gently heated in THF with alkynyl

sulfonamide **100**. Complete consumption of the starting material was observed after one hour at 50 °C. However, upon purification, the product was found not to be the expected **196**, but the result of addition of excess potassium alkoxide to the intermediate ketene, ester **199** in 36% yield (**Scheme 133**). Again, ynol ether formation and [3,3] cyclisation were successful, though the *inter*molecular trapping of the ketene with excess potassium alkoxide proceeded quicker than the *intra*molecular ring closure reaction. Reducing the number of equivalents of alkoxide proved not to be a viable strategy, with very little alkynyl sulfonamide consumed.



Scheme 133

The trapping of the ketene by various nucleophiles arose from the problem of being unable to isolate the initially formed ynol ether **196**, with [3,3] cycloaddition occurring immediately, even at –78 °C. In light of this, it was felt that altering the electronic character of the heteroaromatic ring would allow isolation of the ynol ether. Pyrrole rings were chosen, as altering the nitrogen substituent would allow ready access to both electron rich and deficient ring systems. To study the effect of these two extremes, **200** and **201** (**Figure 8**) were synthesised by methylation and reduction of ethylindole-2-carboxylate, and tosylation then reduction of pyrrole-2-carboxaldehyde respectively.

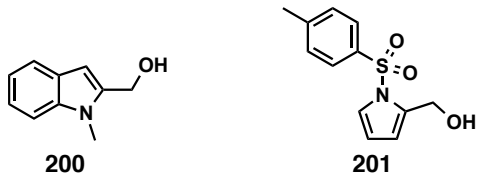
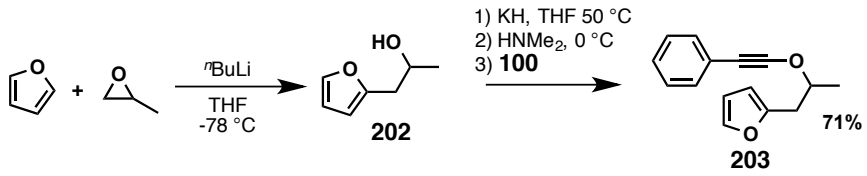


Figure 8

Unfortunately, synthesis of the ynol ether was unsuccessful with both substrates, with only a mixture of degradation products obtained in each case.

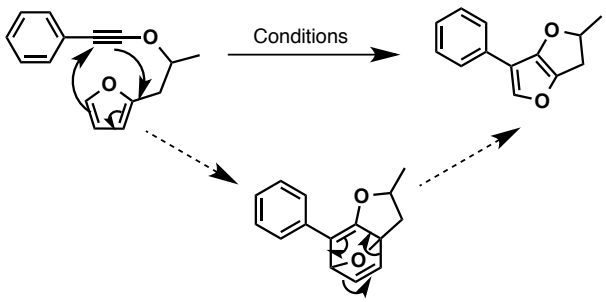
With the synthesis of five-membered rings proving difficult, attention was turned to the synthesis of six-membered rings. Alcohol **202**, prepared *via* the ring opening of propylene oxide by *ortho*-lithiated furan, was used as previously to synthesise ynol ether **203** in 71% yield (**Scheme 134**).



Scheme 134

Pleasingly, **203** could be isolated *via* column chromatography. It was envisaged that **203** could enable access to fused five-membered ring species, and so a number of conditions were attempted in order to gain access to cyclisation products (**Table 15**).

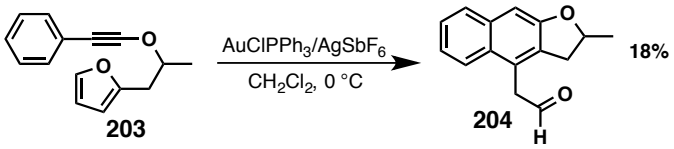
Initial attempts to achieve cyclisation envisaged a thermally driven, *intra*molecular Diels-Alder reaction of **203** (**Table 15**, **Entries 1** and **2**). Only starting material was observed in each case, an unsurprising result when considering the mismatched electron demand of the diene and alkyne, with both being considerably electron rich species.



Entry	Conditions	Product
1	THF, reflux	-
2	Toluene, reflux	-
3	Toluene, NBS (2.0 eq), reflux	Complex mixture
4	Br_2, chlorobenzene, reflux	-
5	$AuClPPh_3/AgSbF_6$, CH_2Cl_2, 0 °C	**204** (18%)
6	$AuClPPh_3/AgBF_4$, CH_2Cl_2, rt	**204** (24%)

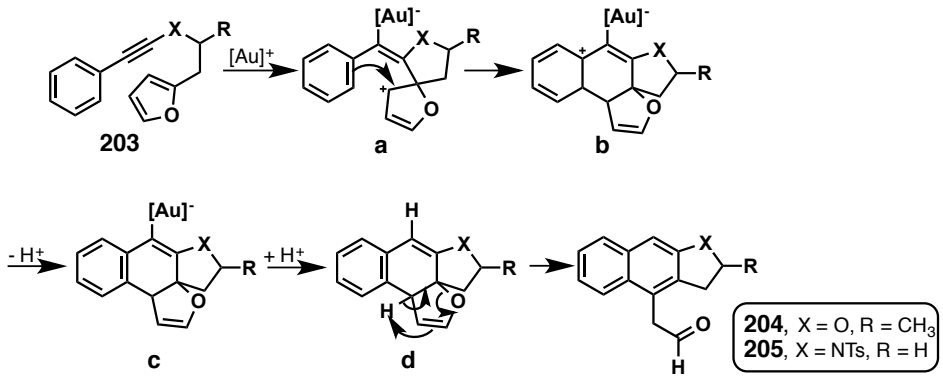
Table 15

Subsequent reactions attempted to exploit the increase in rate and yield often observed in the Diels-Alder reactions of furans that are substituted with halogens.[198] As such, brominating agents were included in reactions (**Table 15**, **Entries 4** and **5**). In the presence of *N*-bromosuccinimide in toluene, a complex mixture of brominated degradation products was observed, and no products could be identified. When ynol ether **203** was refluxed with bromine in chlorobenzene, no consumption of the starting material was observed, and **203** could be recovered.



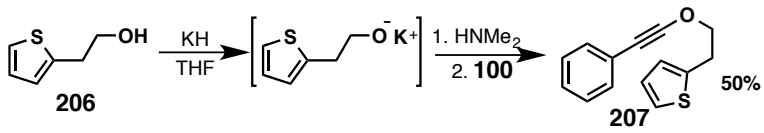
Scheme 135

In order to activate the alkyne towards *intra*molecular attack, the use of pi-acids was subsequently investigated. Under the influence of gold catalysis (**Table 15**, **Entries 5** and **6**), an unexpected dihydrofuran product **204** was isolated (**Scheme 135**). The product closely resembles that synthesised by Hashmi *et al*.[199] in their investigations of analogous ynamides, and opens a route towards interesting naphthalene derivatives under mild reaction conditions. A mechanism to account for the formation of **204** requires initial gold activation of the alkyne of **203**, and 5-*exo* furan cyclisation at the 2-position to give intermediate **203a**. A Friedel-Crafts electrophilic attack gives intermediate **203b**, with cyclised intermediate **203c** formed following rearomatisation. Deauration yields **203d**, which can undergo a second rearomatisation step to yield the dihydrofuran/indole derivatives **204** and **205**. The route employed by Hashmi and co-workers requires a Sonogashira step to introduce the heteroatom-substituted aryl alkyne in the starting material (**Scheme 136**, **203**, **X** = NTs, **R** = H), significantly restricting the scope of substrates available. In contrast, the route towards ynol ethers and alkynyl sulfides developed in the Wilden group would circumvent this problem, allowing access to a considerably broader range of substrates. However, attempts to further optimise the reaction proved unsuccessful, with yields consistently below 25%.



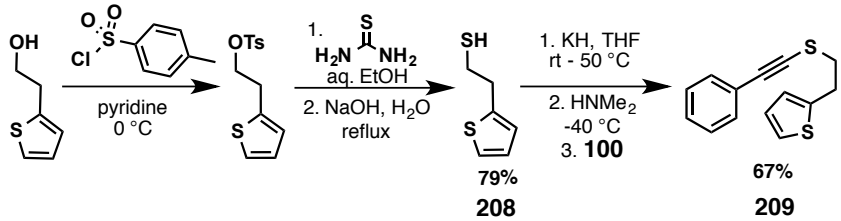
Scheme 136

To further investigate the scope of cyclisation reactions, the furan ring was changed to a thiophene ring. Readily obtained upon the $LiAlH_4$ mediated reduction of 2-thiopheneacetic acid, alcohol **206** was used to synthesise ynol ether **207** as previously in a 50% yield (**Scheme 137**).



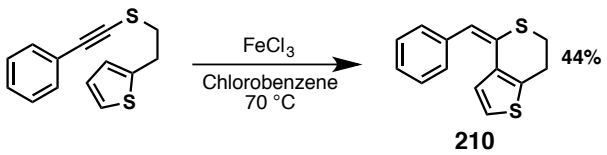
Scheme 137

Unfortunately, subjecting **207** to any of the gold catalysis conditions of **Table 15** resulted in complete starting material degradation, a consequence of the high reactivity of the ynol ether linkage. As alkynyl sulfides are known to be significantly less reactive than ynol ethers, alcohol **206** was converted to thiol **208** by tosylation, followed by reaction with thiourea and treatment with sodium hydroxide (**Scheme 138**).[200] Thioynol ether synthesis according to **Table 13** yielded alkynyl sulfide **209** in 67% yield.



Scheme 138

The stubborn nature of alkynyl sulfides was again evident, however, with no reaction and complete starting material recovery observed under the successful gold catalysis conditions of **Table 15**. A brief scope of transition metal catalysts (Pt(IV), Ru(II), Rh(II), Pd(II), Cu(I), Cu(II), Fe(III)) highlighted an interesting result in the presence of $FeCl_3$, with a product tentatively assigned as **210** isolated in 44% yield (**Scheme 139**). No reaction, or degradation of **209** was observed for all other metal catalysts investigated.



Scheme 139

The carbon-carbon bond forming reaction would suggest that $FeCl_3$ plays a role in activating the alkyne, akin to established pi-Lewis acids such as gold. With reaction under iron mediation established, the reaction with ynols could also be investigated. However, the higher reactivity of the ynol ether again prevented isolation of any identifiable products, with hydration of the alkyne presumed to have occurred. Nevertheless, the synthesis of **210** represents an interesting example of carbon-carbon bond formation.

8.7.2. Ynol Ether Mediated Routes to Cannabinol Core

The biphenyl framework of cannabinol (**Figure 9**) is a common motif in natural product chemistry, and represents an attractive template for further modification.

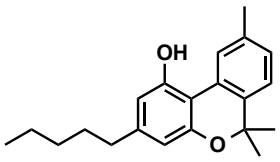
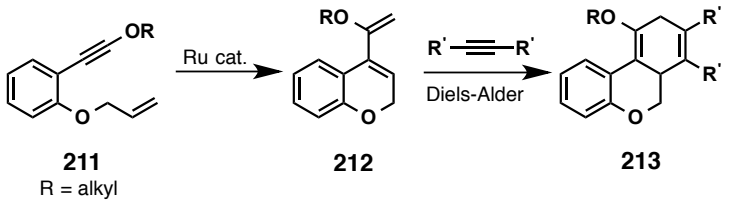


Figure 9

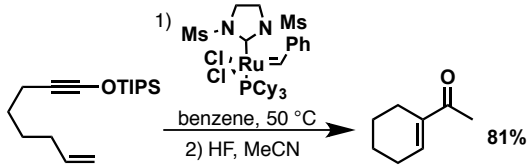
Typical routes towards cannabinols have generally relied upon aromatisation of tetrahydrocannabinols,[201] biaryl formation *via* nucleophilic aromatic substitution,[202] or a Suzuki protocol.[203] It was envisaged that a ring-closing metathesis reaction of ynol ether **211** would generate diene **212**, which would then be able to undergo a Diels-

Alder reaction, affording ready access to the cannabinol core framework **213** (**Scheme 140**).



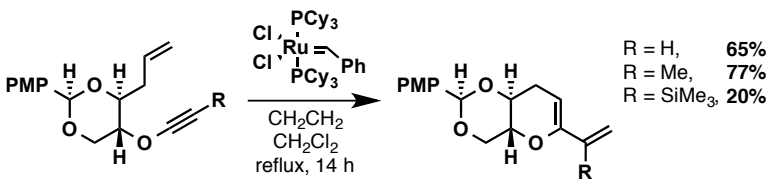
Scheme 140

The use of ynol ethers in metathesis reactions is rare, though a similar ene-yne metathesis reaction has been employed successfully by Kozmin *et al*.[204] in the synthesis of enones from siloxyalkynes (**Scheme 141**). The reaction is tolerant of a range of functional groups and ene-yne tether lengths, affording enones in excellent yields under mild conditions.



Scheme 141

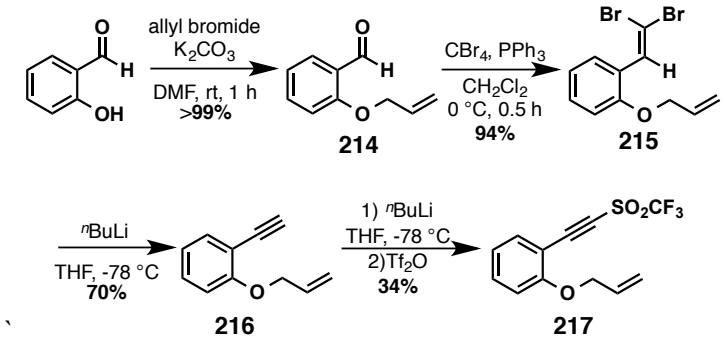
Clark *et al*.[205] have also shown that alkynyl ethers are suitable substrates for ring closing metathesis reactions, allowing access to the cyclic ether building blocks of many natural products. Cyclisation mediated by Grubbs' first generation catalyst allowed access to the ring closed substrates in acceptable to good yields (**Scheme 142**).



Scheme 142

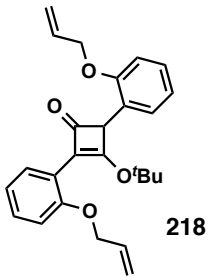
Previous work in the group has shown that sulfinamide oxidation in the presence of an allyl group is not a viable pathway, and a convoluted protecting group strategy

towards ynol ether **211** is required.[206] Therefore, in order to reduce the number of steps required, the sulfonamide unit was replaced with a triflate group. 2-Allyloxybenzaldehyde **214** was formed quantitatively by reaction of salicylaldehyde with allyl bromide and potassium carbonate. Standard Corey-Fuchs conditions were employed to synthesise dibrominated compound **215**, which formed terminal alkyne **216** upon treatment with ^{n}BuLi. Deprotonation of **216** and treatment with triflic anhydride yielded alkynyl sulfone **217** in 34% yield (**Scheme 143**). The final two steps could be conducted in a single pot, though in this case, the product proved difficult to separate from an unknown by-product.



Scheme 143

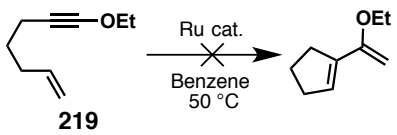
When using alkynyl triflate **217**, a secondary amine was not required for ynol ether formation, a result of the strong electron withdrawing capacity of the sulfone. Ynol ether formation with potassium *tert*-butoxide proceeded as previously, with a clear product visible *via* TLC. However, the product was not stable to work-up or column chromatography, with rapid degradation observed. This is possibly a result of a [3,3] sigmatropic rearrangement forming a ketene, and subsequent *inter*molecular [2+2] cycloaddition with another alkyne to yield a dimer **218** (*c.f* **Scheme 128**; **Figure 10**). Indeed, peaks that could correspond to such a molecule were observed by NMR, though further degradation prevented confirmation. The formation of dimer **218** suggests that ynol ether formation occurs successfully, followed by preferential rearrangement according to **Scheme 128**, rather than *intra*molecular cyclisation with the allyl unit. Bypassing purification, attempts at *in situ* metathesis reactions using both Grubbs' 1st and Grubbs' 2nd generation catalysts failed to produce any isolable products.



218

Figure 10

Potassium methoxide, freshly prepared *via* reaction of methanol and potassium metal in THF, was used subsequently for ynol ether formation. The methoxy group is unable to undergo the same [3,3] rearrangement as the *tert*-butyl group, allowing the isolation of **211** (**Scheme 140**, R = Me) in 42% yield. However, metathesis reactions again proved unsuccessful, with complete degradation of **211** observed in the presence of both Grubbs' 1st and Grubbs' 2nd generation catalysts. In addition, neither prolonged heating nor irradiation with UV light (λ = 365 nm) could promote a [2+2] cyclisation to occur, with no reaction or complete degradation observed respectively. Kozmin *et al*.[204] have also noted the failure of ene-yne metathesis reactions with ynol ether substrates. In their hands, ethoxyalkyne **219** produced no detectable amount of the corresponding diene, even when using forcing conditions (**Scheme 144**).



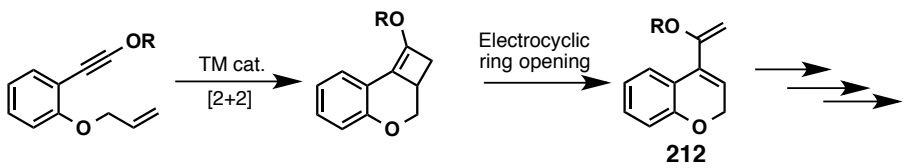
219

Scheme 144

9. Conclusions and Future Work

The combination of a strong base such as potassium *tert*-butoxide with a secondary amine or phenanthroline derivative has become a common mixture in transition metal-free reactions, often with little appreciation of the role played by the additive. The work presented in this thesis has shown that the combination can be regarded as a potent source of reducing power, readily transferring an electron to suitable substrates. When 1,10-phenanthroline is included as the additive, reactions proceed *via* an initial single electron transfer to phenanthroline, which behaves as a temporary sink for electrons. When secondary amines such as DMEDA are used as additives, the increased reactivity is believed to be due to the stabilisation of an intermediate alkoxy radical by hydrogen bonding. In the absence of additives, the single greatest contribution towards reaction success is the degree of dissociation of metal alkoxides.

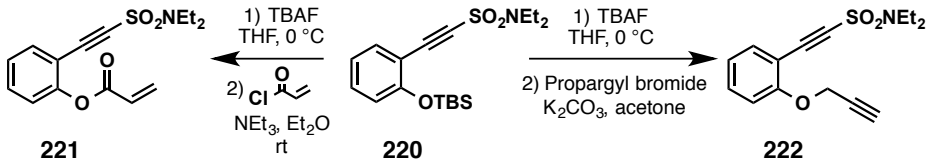
The reducing environment has been exploited to gain access to a number of substrates that would otherwise generally rely upon transition metal mediation. In synthesising heteroatom substituted alkynes, ready access to alkynyl sulfides and ynol ethers, both useful synthetic intermediates, has been established. Further work in this area will continue to exploit the high reactivity of these understudied, substituted alkynes. Particularly interesting is the propensity of ynol ethers to undergo [2+2] cyclisation reactions.[140] Whilst initial investigations towards the synthesis of the cannabinol core failed at the crucial [2+2] cyclisation step, further investigation into a metal catalysed reaction could provide access to the crucial intermediate **212**, with a further Diels-Alder reaction allowing access to the common skeleton (**Scheme 145**).



Scheme 145

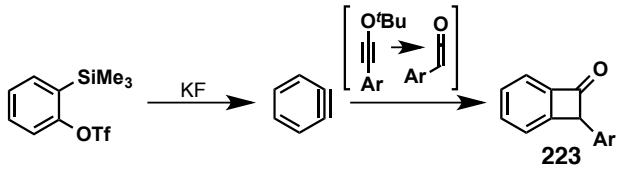
Alternatively, the electronic demand of the allyl unit could be investigated, so as to favour *intra*molecular reaction. As such, molecules **221** and **222** could be prepared

from a common intermediate **220** (**Scheme 146**), and represent alternative electron demands compared to **211**. Ynol ether formation could then proceed as previously.



Scheme 146

In addition, reaction of ynol ethers with benzynes may give access to interesting benzocyclobutenone products **223**, which are powerful intermediates in organic synthesis, being highly susceptible to further transformation (**Scheme 147**).[207,208]



Scheme 147

10. Experimental

All reactions were carried out at atmospheric pressure, in flame-dried glassware under an atmosphere of argon unless otherwise stated. Reagents and solvents were purchased from suppliers and used as received unless noted otherwise. Normal phase silica gel (Merck Kieselgel 60) 0.04/0.063 (230–400 mesh) was used for flash column chromatography. Reaction progress was monitored *via* TLC analysis, using aluminium plates pre-coated with silica gel 60 F_{254}, and visualised by combination of UV (254 nm) and potassium permanganate chemical stain with heating. Solvent removal *in vacuo* refers to rotary evaporation at 18–50 °C, using a house vacuum operating at approximately 10 mmHg. Room temperature is defined as 19–23 °C.

^{1}H NMR were recorded at 500 MHz or 600 MHz using a Bruker AMX500 or AMX600 instrument respectively, operating at ambient temperature. ^{13}C NMR spectra were recorded at 125 or 150 MHz using a Bruker AMX500 or Bruker AMX600 MHz spectrometer respectively. Chemical shifts are reported in parts per million, and are referenced to the proton impurity of deuterated solvents. Coupling constants (*J*) are reported in Hertz (Hz). The multiplicity of a given signal is reported as s (singlet), d (doublet), t (triplet), q (quartet), quint. (quintet), sext. (sextet), dd (doublet of doublets) or td (triplet of doublets). In cases where complex signals make determination of the multiplicity difficult, peaks are defined as m (multiplet). Infrared spectra were recorded as thin films using a FTIR Perkin Elmer Spectrum 100, operating in ATR mode. Mass spectra were measured on a Thermo Finnigan MAT900 XP operating in EI and CI mode. ESI spectra were measured on a Waters LCT premier XE LC-TOF mass spectrometer. Melting points were measured using Gallenkamp apparatus and are uncorrected.

Purification of commercial 1,10-phenanthroline

1,10-Phenanthroline (3.0 g, 16.6 mmol, 1.0 eq) purchased from Alfa Aesar (anhydrous, 99%) was dissolved in CH_2Cl_2 (100 mL). To the solution was added methanesulfonic acid (3.2 g, 33.3 mmol, 2.0 eq). The mixture was subsequently washed with aqueous ammonia solution (28% solution in water, 3 x 100 mL). The organic layer was separated, dried over $MgSO_4$ and filtered. Concentration *in vacuo* yielded a white solid. The crude reaction mixture was recrystallised (CH_3Cl) to give the purified product, which was stored in a vacuum oven (40 °C) between use.

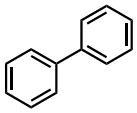
Colourless plates, 77%; m.p.; 115–116 °C (lit. 118 °C from PE)[a]. M.p. prior to purification was 90–99 °C.

General Procedure A: Synthesis of biaryls 103a–103h

Potassium *tert*-butoxide (101 mg, 0.90 mmol, 4.0 eq), aryl iodide (0.23 mmol, 1.0 eq) and benzene (2.4 mL, 120 eq) were stirred at 160 °C for 6 h in a flame-dried, pressure resistant tube that had been backflushed with argon. Upon cooling to rt, the crude reaction material was quenched with 1 M aqueous HCl solution (5 mL), then diluted with Et_2O (5 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with saturated sodium chloride solution (10 mL) and dried over $MgSO_4$. The organic portion was filtered, concentrated *in vacuo* and purified *via* column chromatography (100% PE, or as indicated) to yield biaryls **103a–103h**.

[a] Cumper, C. W. N.; Ginman, R. F. A.; Vogel, A. I., *J. Chem. Soc.*, **1962**, 1188

Biphenyl 103a

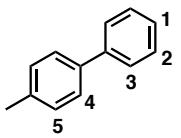


Synthesised using iodobenzene, according to general procedure **A**.

White solid, 77%; m.p.; 69–70 °C (lit. 69–70 °C)[b]; ν_{max} (film)/cm^{-1} 3029, 1596, 1481, 1430, 1073, 1008, 902; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.60 (d, J = 7.8 Hz, 4H, 2 x *o*-Ar*H*), 7.45 (t, J = 7.6 Hz, 4H, 2 x *m*-Ar*H*), 7.35 (t, J = 7.1 Hz, 2H, 2 x *p*-Ar*H*); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 141.3 (C_q), 128.9 (CH), 127.4 (CH), 127.3 (CH); LRMS (EI) 154 (100), 128 (4), 115 (4) 76 (5).

Data in agreement with literature values.[c]

4-Methylbiphenyl 103b



Synthesised using 4-iodotoluene, according to general procedure **A**.

White solid, 66%; m.p.; 45–46 °C (lit. 46 °C)[d]; ν_{max} (film)/cm^{-1} 3025, 2919, 2854, 1600, 1517, 1485, 906; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.60 (d, J = 8.3 Hz, 2H, **3**-Ar*H*), 7.51 (d, J = 8.0 Hz, 2H, **4**-Ar*H*), 7.44 (t, J = 7.6 Hz, 2H, **2**-Ar*H*), 7.34 (t, J = 7.5 Hz, 1H, **1**-Ar*H*), 7.27 (d, J = 8.0 Hz, 2H, **5**-Ar*H*), 2.41 (s, 3H, (C)CH_3); ^{13}C NMR (150 MHz, $CDCl_3$)* δ_C 141.3 (C_q), 138.5 (C_q), 137.2 (C_q), 129.6 (CH), 128.8 (CH), 127.1 (CH), 127.1 (CH), 21.2 (CH_3); LRMS (EI) 168 (100), 167 (52), 152 (18), 115 (6), 91 (4). *Two signals are coincident

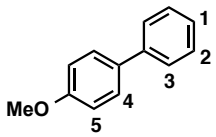
Data in agreement with literature values.[c]

[b] Chan, K. C.; Ruang, R. L., *J. Chem. Soc.*, **1965**, 2649

[c] Budén, M. E.; Guastavino, J. F.; Rossi, R. A. *Org. Lett.*, **2013**, *15*, 1174

[d] Mino, T.; Shirae, Y.; Sakamoto, M.; Fujita, T., *J. Org. Chem.*, **2005**, 2191

4-Methoxybiphenyl 103c

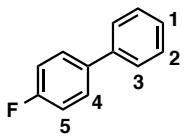


Synthesised using 4-iodoanisole, according to general procedure **A**.

White solid, 48%; m.p.; 84–85 °C (lit. 84–85 °C)[e]; ν_{max} (film)/cm^{-1} 3030, 2999, 2834, 1608, 1517, 1462, 1244, 1175, 1034, 903; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.57–7.53 (m, 4H, **3**- and **4**-Ar*H*), 7.42 (t, *J* = 7.6 Hz, 2H, **2**-Ar*H*), 7.31 (t, *J* = 7.4 Hz, 1H, **1**-Ar*H*), 6.99 (d, *J* = 8.8 Hz, 2H, **5**-Ar*H*), 3.86 (s, 3H, OCH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 159.2 (C_q), 140.9 (C_q), 133.9 (C_q), 128.8 (CH), 128.3 (CH), 126.9 (CH), 126.8 (CH), 114.3 (CH), 55.5 (CH_3); LRMS (EI) 184 (100), 169 (31), 152 (7), 141 (37), 115 (29).

Data in agreement with literature values.[c]

4-Fluorobiphenyl 103d



Synthesised using 4-fluoroiodobenzene, according to general procedure **A**.

White solid, 64%; m.p.; 69–70 °C (lit. 69 °C)[f]; ν_{max} (film)/cm^{-1} 3060, 3031, 2924, 1596, 1515, 1482, 1450, 1231, 1194, 1107, 906; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.56–7.54 (m, 4H, **3**- and **4**-Ar*H*), 7.44 (t, *J* = 7.5 Hz, 2H, **2**-Ar*H*), 7.35 (m, 1H, **1**-Ar*H*), 7.13 (t, *J* = 8.6 Hz, 2H, **5**-Ar*H*); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 163.4 and 161.8 (d, *J* = 245.9 Hz) (C_q), 140.4 (C_q), 137.4 (d, *J* = 3.2 Hz) (C_q), 128.9 (CH), 128.8 (d, *J* = 8.0 Hz) (CH), 127.4 (CH), 127.1 (CH), 115.7 (d, *J* = 21.3 Hz) (CH); LRMS (EI) 172 (100), 152 (5).

Data in agreement with literature values.[c]

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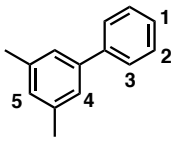
[e] Kuriyama, M.; Matsuo, S.; Onomura, O.; Shinozawa, M., *Org. Lett.*, **2013**, 2716

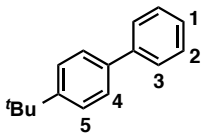
[f] Allred, A. L.; Bush, L. W., *Tetrahedron*, **1968**, 6883

3,5-Dimethylbiphenyl 103e



Synthesised using 3,5-dimethyliodobenzene, according to general procedure **A**.
Colourless oil, 48%; ν_{max} (film)/cm^{-1} 3026, 2913, 1600, 1575, 1495, 1463, 1374, 1073, 1031; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.58 (dd, J = 8.3, 1.3 Hz, 2H, **3**-Ar*H*), 7.42 (t, J = 7.5 Hz, 2H, **2**-Ar*H*), 7.33 (t, J = 7.4 Hz, 1H, **1**-Ar*H*), 7.21 (br s, 2H, **4**-Ar*H*), 7.00 (br s, 1H, **5**-Ar*H*), 2.38 (s, 6H, 2 x (C)CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 141.6 (C_q), 141.4 (C_q), 138.4 (C_q), 129.0 (CH), 128.7 (CH), 127.3 (CH), 127.2 (CH), 125.2 (CH), 21.5 (CH_3); LRMS (EI) 182 (100), 167 (36), 152 (11), 115 (5).
Data in agreement with literature values.[g]

4-*tert*-Butylbiphenyl 103f



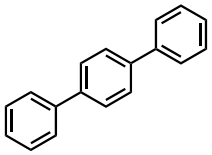
Synthesised using 4-*tert*-butyliodobenzene, according to general procedure **A**.
White solid, 30%; m.p.; 48–49 °C (lit. 48–49 °C)[h]; ν_{max} (film)/cm^{-1} 2962, 1485, 1394, 1363, 1267, 1112, 1006, 902; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.60 (d, J = 7.2 Hz, 2H, **3**-Ar*H*), 7.55 (d, J = 8.4 Hz, 2H, **4**-Ar*H*), 7.47 (d, J = 8.4 Hz, 2H, **5**-Ar*H*), 7.43 (t, J = 7.5 Hz, 2H, **2**-Ar*H*), 7.33 (t, J = 7.3 Hz, 1H, **1**-Ar*H*), 1.37 (s, 9H, (C)(CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 150.3 (C_q), 141.1 (C_q), 138.4 (C_q), 128.7 (CH), 127.1 (CH), 127.0 (CH), 126.8 (CH), 125.8 (CH), 34.6 (C_q), 31.4 (CH_3); LRMS (EI) 210 (36), 195 (100), 178 (11), 167 (19), 152 (9), 115 (4).
Data in agreement with literature values.[i]

[g] Li, X.; Yan, X. -Y.; Chang. H. -H.; Wang, L. -C.; Zhang, Y.; Chen, W. W.; Li, Y. -W.; Wei, W. -L., *Org. Biomol. Chem.*, **2012**, *10*, 495

[h] Fan, X. -H.; Yang, L. -M., *Eur. J. Org. Chem.*, **2010**, *13*, 2457

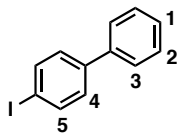
[i] Iglesias, M. J.; Prieto, A.; Nicasio, M. C., *Org. Lett.*, **2012**, *14*, 4318

***p*-Terphenyl 103ga**



Synthesised using 1,4-diiodobenzene, according to general procedure **A**.
White solid, 21%; m.p.; 212–213 °C (lit. 212–213 °C)[d]; ν_{max} (film)/cm^{-1} 3053, 3023, 2919, 1475, 1453, 1402, 1258, 1190, 1167, 1074, 1000, 836; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.68 (s, 4H, centre ring Ar*H*), 7.65 (d, *J* = 7.1 Hz, 4H, 2 x *o*-Ar*H*), 7.46 (t, *J* = 7.4 Hz, 4H, 2 x *m*-Ar*H*), 7.36 (t, *J* = 7.4 Hz, 2H, 2 x *p*-Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 140.8 (C_q), 140.2 (C_q), 128.9 (CH), 127.6 (CH), 127.4 (CH), 127.1 (CH); LRMS (EI) 230 (100), 195 (15), 152 (13), 115 (9).
Data in agreement with literature values.[c]

4-Iodobiphenyl 103gb

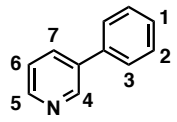


Synthesised using 1,4-diiodobenzene, according to general procedure **A**.
White solid, 30%; m.p.; 107–108 °C (lit. 109–110 °C)[j]; ν_{max} (film)/cm^{-1} 3051, 3027, 2921, 1470, 1387, 1063, 995; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.77 (m, 2H, **5**-Ar*H*), 7.55 (m, 2H, **3**-Ar*H*), 7.44 (m, 2H, **2**-Ar*H*), 7.38–7.32 (m, 3H, **1**- and **4**-Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 140.8 (C_q), 140.1 (C_q), 137.9 (CH), 129.1 (CH), 129.0 (CH), 127.8 (CH), 127.0 (CH), 93.1 (C_q); LRMS (EI) 280 (100), 152 (55).
Data in agreement with literature values.[k]

[j] Qin, Y.; Wei, W.; Luo, M., *Synlett*, **2007**, 2410

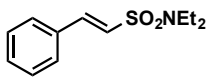
[k] Kulbitski, K.; Nisnevich, G.; Gandelman, M., *Adv. Synth. Catal.*, **2011**, *353*, 1438

3-Phenylpyridine 103h



Synthesised using 3-iodopyridine, according to general procedure **A** (Purified *via* column chromatography using 0–2% MeOH/CH_2Cl_2 as eluent).
Colourless oil, 37%; ν_{max} (film)/cm^{-1} 3056, 2921, 2850, 1722, 1450, 1407, 1263, 1120, 1098; NMR (600 MHz, $CDCl_3$) δ_H 8.87 (br s, 1H, **4**-Ar*H*), 8.61 (br s, 1H, **5**-Ar*H*), 7.89 (dt, *J* = 7.9, 1.7 Hz, 1H, **7**-Ar*H*), 7.59 (d, *J* = 7.1 Hz, 2H, **3**-Ar*H*), 7.49 (t, *J* = 7.5 Hz, 2H, **2**-Ar*H*), 7.43–7.37 (m, 2H, **1**- and **6**-Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 148.5 (CH), 148.3 (CH), 137.9 (C_q), 136.9 (C_q), 134.6 (CH), 129.2 (CH), 128.2 (CH), 127.3 (CH), 123.8 (CH); LRMS (EI) 155 (100), 127 (8), 115 (3).
Data in agreement with literature values.[c]

(*E*)-*N*,*N*-Diethyl-2-phenylethene-1-sulfonamide 121

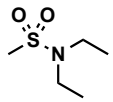


A flask was charged with a stirrer bar, *trans*-*β*-styrene sulfonyl chloride (2.5 g, 12.3 mmol, 1.0 eq) and CH_2Cl_2 (30 mL). The mixture was cooled to 0 °C, and *N*,*N*-diethylamine (2.6 mL, 24.7 mmol, 2.0 eq) was added dropwise. The reaction was allowed to warm to rt, and stirred for 30 min. Upon complete conversion of starting material, the crude reaction mixture was diluted with CH_2Cl_2 (100 mL), and washed with water (50 mL) and brine (50 mL). The organic component was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (0–10% EtOAc/PE) yielded **121**.

Waxy white solid, 82%; ν_{max} (film)/cm^{-1} 3041, 2969, 2931, 1609, 1447, 1317, 1198, 1132, 1014; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.49–7.47 (m, 2H, *o*-Ar*H*), 7.44 (d, *J* = 15.4 Hz, 1H, ArC*H*), 7.42–7.40 (m, 3H, *m*- and *p*-Ar*H*), 6.66 (d, *J* = 15.4 Hz, ArCHC*H*), 3.28 (q, *J* = 7.1 Hz, 4H, 2 x NCH_2CH$_3$), 1.22 (t, *J* = 7.1 Hz, 6H, 2 x

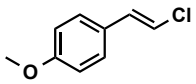
NCHCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 140.9 (CH), 133.0 (C_q), 130.7 (CH), 129.2 (CH), 128.2 (CH), 124.9 (CH), 41.9 (CH_2), 14.6 (CH_3); LRMS (EI) 239 (27), 224 (100), 167 (99), 103 (95); HRMS (EI) calc'd for $C_{12}H_{17}NO_2S$ (M^+) 239.0975, found 239.0974.

_N_,_N_-Diethylmethanesulfonamide 123



Colourless oil, 28%; ν_{max} (film)/cm^{-1} 2974, 2935, 1462, 1317, 1198, 1138, 1016; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 3.28 (q, J = 7.1 Hz, 4H, 2 x NCH_2CH$_3$), 2.83 (s, 3H, SCH_3), 1.21 (t, J = 7.1 Hz, 2 x NCH$_2$CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 41.8 (CH_2), 38.9 (CH_3), 14.3 (CH_3); LRMS (EI) 151 (13), 136 (100), 108 (13).
Data in agreement with literature values.[l]

(_E_)-1-(2-Chlorovinyl)-4-methoxybenzene 125



In a vessel open to the atmosphere, (*E*)-3-(4-methoxyphenyl)acrylic acid (400 mg, 2.2 mmol, 1.0 eq) was dissolved in CH_2Cl_2 (15 mL). Triethylamine (16 μL, 0.1 mmol, 0.05 eq) was added, and the mixture stirred at rt for 5 min. To the solution was added *N*-chlorosuccinimide (360 mg, 2.7 mmol, 1.2 eq, recrystallised from hot water and dried overnight in a vacuum oven at 40 °C), and the mixture was stirred for a further 5 min at rt. The solvent was removed *in vacuo*, and the crude mixture purified *via* column chromatography (0–2% EtOAc/PE) to afford **125**.[m]

Colourless oil, 91%; ν_{max} (film)/cm^{-1} 3070, 2960, 2934, 2838, 1603, 1509, 1303, 1238, 1174, 1026, 946; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.23 (d, J = 8.8 Hz, 2H, O(C)CHCH),

[l] Banks, M. R.; Hudson, R. F., *J. Chem. Soc. Perkin Trans. 2*, **1986**, 151

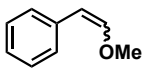
[m] Das, J. P.; Roy, S., *J. Org. Chem.*, **2002**, *67*, 7861

6.85 (d, J = 8.8 Hz, 2H, O(C)C*H*), 6.77 (d, J = 13.5 Hz, 1H, ClCHC*H*), 6.50 (d, J = 13.5 Hz, 1H, ClC*H*CH), 3.81 (s, 3H, OCH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 159.7 (C_q), 132.8 (CH), 127.7 (C_q), 127.5 (CH), 116.5 (CH), 114.3 (CH), 55.4 (CH_3); LRMS (EI) 170 (34), 168 (100), 155 (18), 153 (53), 133 (11), 125 (30).
Data in agreement with literature values.[n]

General Procedure B: Synthesis of enol ethers 126a–126j

In a flame-dried, sealed tube under an atmosphere of argon, potassium methoxide (67 mg, 0.96 mmol, 4.0 eq), *N*,*N*'-dimethylethylenediamine (50 μL, 0.48 mmol, 2.0 eq) and terminal acetylene (0.24 mmol, 1.0 eq) were mixed with anhydrous DMF (1.5 mL). The mixture was gently heated to 55 °C (unless stated otherwise) and stirred for 15 h. The reaction mixture was then allowed to cool to rt, and quenched *via* the addition of water (2 mL). The crude mixture was diluted with CH_2Cl_2 (100 mL) and washed with saturated LiCl solution (3 x 20 mL). The organic portions were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification *via* column chromatography (0–5% EtOAc/PE) yielded enol ethers **126a**–**126j**. *Z*:*E* ratios were determined by comparison of NMR integrals, and are quoted for reactions conducted at 55 °C, unless otherwise stated.

(2-Methoxyvinyl)benzene *Z*-126a and *E*-126a



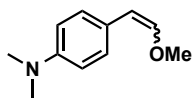
Synthesised using phenylacetylene, according to general procedure **B**.
Z:*E* = 68:32. *E* and *Z* isomers were separated *via* column chromatography, 70% combined yield;
***Z*-126a**: colourless oil; ν_{max} (film)/cm^{-1} 2926, 2862, 1649, 1491, 1454, 1442, 1399, 1299, 1269, 1202; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.57 (d, J=7.2 Hz, 2H, *o*-ArH), 7.29 (t, J=7.6 Hz, 2H, *m*-Ar*H*), 7.15 (t, J=7.3 Hz, 1H, *p*-Ar*H*), 6.15 (d, J=7.0 Hz, 1H, CH_3OCH), 5.23 (d, J=7.0 Hz, 1H, CH_3OCHCH), 3.19 (s, 3H, CH_3O); ^{13}C NMR

[n] Heinrich, M. R.; Blank, O.; Ullrich, D.; Kirschstein, M., *J. Org. Chem.*, **2007**, *72*, 9609

(150 MHz, $CDCl_3$) δ_C 148.1 (CH), 136.0 (C_q), 128.3* (2 x CH), 125.9 (CH), 105.8 (CH), 60.8 (CH_3); LRMS (CI) 135 (100), 91 (8), 85 (3). * Two overlapping peaks

***E*-126a**: Colourless oil; ν_{max} (film)/cm^{-1} 3023, 2933, 2832, 1638, 1599, 1575, 1492, 1450, 1329, 1235, 1190, 1148, 1122; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.28–7.23 (m, 4H, *o*- and *m*-Ar*H*), 7.14 (t, *J*=7.1 Hz, 1H, *p*-Ar*H*), 7.06 (d, *J*=13.0 Hz, 1H, CH_3OCH), 5.82 (d, *J*=13.0 Hz, 1H, CH_3OCHCH), 3.69 (s, 3H, CH_3O); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 149.0 (CH), 136.4 (C_q), 128.7 (CH), 125.8 (CH), 125.2 (CH), 105.1 (CH), 56.6 (CH_3); LRMS (EI) 135 (6), 122 (33), 105 (100), 91 (16).
Data in agreement with literature values.[o]

4-(2-Methoxyvinyl)-*N*,*N*-dimethylaniline *Z*-126b and *E*-126b

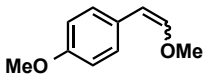


Synthesised using 4-ethynyl-*N*,*N*-dimethylaniline, according to general procedure **B**. *Z*:*E* = 95:5 (*Z*:*E* = 80:20 when the reaction was conducted at 100 °C). *E* and *Z* isomers could not be separated *via* column chromatography, and data was obtained from a mixture.
Pale yellow oil, 47%;[p] ν_{max} (film)/cm^{-1} 2927, 1648, 1605, 1517, 1443, 1396, 1347, 1264, 1188, 1088; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H (***Z*-126b**) 7.47 (d, *J*=8.9 Hz, 2H, N(C)CHC*H*), 6.70 (d, *J*=8.9 Hz, 2H, N(C)C*H*), 6.00 (d, *J*=7.0 Hz, 1H, CH_3OCH), 5.15 (d, *J*=7.0 Hz, 1H CH_3OCHCH), 3.74 (s, 3H, OCH_3), 2.93 (s, 6H, 2×NCH_3); ^{1}H NMR (600 MHz, $CDCl_3$) δ_H (***E*-126b**) 7.13 (d, *J*=8.8 Hz, 2H, N(C)CHC*H*), 6.90 (d, *J*=13.0 Hz, 1H, CH_3OCH), 6.70–6.69 (m, 2H, N(C)C*H*), 5.77 (d, *J*=13.0 Hz, 1H, CH_3OCHCH), 3.65 (s, 3H, OCH_3), 2.92 (s, 6H, 2×NCH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C (***Z*-126b**)148.8 (C_q), 145.4 (CH), 129.2 (CH), 124.9 (Cq), 112.7 (CH), 105.8 (CH), 60.5 (CH_3), 40.9 (CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C (***E*-126b**) 149.2 (C_q), 146.6 (CH), 126.1 (CH), 124.9 (C_q), 113.3 (CH), 105.1 (CH), 56.6 (CH_3), 41.0 (CH_3); HRMS (ESI) calc'd for $C_{11}H_{15}NO$ (M+H) requires 178.1232, found 178.1231.

[o] Kondo, M.; Kochi, T.; Kakiuchi, F., *J. Am. Chem. Soc.*, **2011**, *133*, 32

[p] Reaction conducted at 100 °C

1-Methoxy-4-(2-methoxyvinyl)benzene *Z*-126c and *E*-126c



Synthesised using 4-ethynylanisole, according to general procedure **B**.

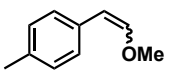
Z:*E* = 91:9 (*Z*:*E* =84:16 when the reaction was conducted at 75 °C). *E* and *Z* isomers were separated *via* column chromatography, 69% combined yield;[q]

***Z*-126c**: Colourless oil, ν_{max} (film)/cm^{-1} 2930, 2831, 1649, 1603, 1571, 1507, 1453, 1397, 1239, 1175, 1089, 1029; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.51 (d, *J*=8.8 Hz, 2H, O(C)CHC*H*), 6.83 (d, *J*=8.8 Hz, 2H, O(C)*CH*), 6.05 (d, *J*=7.0 Hz, 1H, CH_3OCH), 5.18 (d, *J*=7.0 Hz, 1H, CH_3OCHCH), 3.80 (s, 3H, $CH_3O(C)$), 3.76 (s, 3H, CH_3OCH); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 157.7 (C_q), 146.5 (CH), 129.5 (CH), 128.8 (C_q), 113.7 (CH), 105.3 (CH), 60.6 (CH_3), 55.3 (CH_3); LRMS (CI) 165 (100), 150 (12), 135 (4), 121 (6).

***E*-126c**: White solid; MP=45–46 °C; ν_{max} (film)/cm^{-1} 2954, 2937, 2835, 1658, 1637, 1604, 1574, 1508, 1460, 1337, 1286, 1236, 1178; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.16 (d, *J*=8.7 Hz, 2H, O(C)CHC*H*), 6.93 (d, *J*=13.0 Hz, 1H, CH_3OCH), 6.82 (d, *J*=8.7 Hz, 2H, O(C)C*H*), 5.78 (d, *J*=13.0 Hz, 1H, CH_3OCHCH), 3.79 (s, 3H, $CH_3O(C)$), 3.66 (s, 3H, CH_3OCH); ^{13}C NMR (150 MHz, CD_2Cl_2) δ_C 157.9 (C_q), 147.5 (CH), 128.9 (C_q), 126.0 (CH), 114.0 (CH), 104.3 (CH), 56.4 (CH_3), 55.2 (CH_3); LRMS (EI) 164 (81), 149 (45), 121 (100), 91 (16).

Data in agreement with literature values.[o]

1-(2-Methoxyvinyl)-4-methylbenzene *Z*-126d and *E*-126d



Synthesised using 4-ethynyltoluene, according to general procedure **B**.

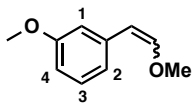
[q] Reaction conducted at 75 °C

Z:*E* = 80:20. *E* and *Z* isomers were separated *via* column chromatography, 66% combined yield;

***Z*-126d**: Colourless oil; ν_{max} (film)/cm^{-1} 2840, 1730, 1684, 1600, 1579, 1509, 1443, 1426, 1398, 1354, 1303, 1256, 1243; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.46 (d, *J*=8.0 Hz, 2H, CH_3(C)CHC*H*), 7.10 (d, *J*=8.0 Hz, 2H, CH_3(C)C*H*), 6.09 (d, *J*=7.0 Hz, 1H, CH_3OC*H*), 5.20 (d, *J*=7.0 Hz, 1H, CH_3OCHC*H*), 3.77 (s, 3H, C*H*$_3$O), 2.32 (s, 3H, C*H*$_3$(C)); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 147.4 (CH), 135.5 (C_q), 133.1 (C_q), 129.0 (CH), 128.2 (CH), 105.7 (CH), 60.7 (CH_3), 21.3 (CH_3); LRMS (EI) 148 (54), 133 (11), 119 (11), 105 (41), 86 (64), 84 (100).

***E*-126d**: Colourless oil (contaminated with 9% *Z*-isomer); ν_{max} (film)/cm^{-1} 2922, 2852, 1637, 1512, 1461, 1336, 1317, 1297, 1236, 1189, 1149; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.13 (d, *J*=8.0 Hz, 2H, CH_3(C)CHC*H*), 7.08 (d, *J*=8.0 Hz, 2H, CH_3(C)C*H*), 7.01 (d, *J*=13.0 Hz, 1H, CH_3OC*H*), 5.80 (d, *J*=13.0 Hz, 1H, CH_3OCHC*H*), 3.68 (s, 3H, C*H*$_3$OCH), 2.31 (s, 3H, C*H*$_3$(C)); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 148.3 (CH), 135.4 (C_q), 133.2 (C_q), 129.4 (CH), 125.1 (CH), 105.0 (CH), 56.6 (CH_3), 21.2 (CH_3). Data in agreement with literature values.[o]

1-Methoxy-3-(2-methoxyvinyl)benzene *Z*-126e and *E*-126e



Synthesised using 3-ethynylanisole, according to general procedure **B**.

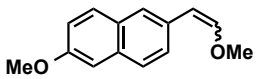
Z:*E* = 60:40. *E* and *Z* isomers were separated *via* column chromatography, 72% combined yield;

***Z*-126e**: colourless oil; ν_{max} (film)/cm^{-1} 2936, 2831, 1649, 1597, 1573, 1484, 1455, 1428, 1399, 1256, 1238, 1165, 1094; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.21–7.19 (m, 2H, **2**,**3**-Ar*H*), 7.12–7.11 (m, 1H, **1**-Ar*H*), 6.71 (ddd, *J*=8.2, 2.7, 0.8 Hz, 1H, **4**-Ar*H*), 6.14 (d, *J*=6.9 Hz, 1H, CH_3OC*H*), 5.20 (d, *J*=6.9 Hz, 1H, CH_3OCHC*H*), 3.80 (s, 3H, C*H*$_3$O(C)), 3.78 (s, 3H, C*H*$_3$OCH); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 159.5 (C_q), 148.3 (CH), 137.3 (C_q), 129.2 (CH), 121.0 (CH), 113.7 (CH), 111.6 (CH), 105.6 (CH), 60.9

(CH_3), 55.3 (CH_3); LRMS (CI) 164 (85), 149 (3), 121 (40), 91 (17), 86 (64), 84 (100); HRMS (EI) calc'd for $C_{10}H_{12}O_2$ (M^+) requires 164.0837, found 164.0835.

***E*-126e**: Colourless oil (contaminated with 18% *Z*-isomer); ν_{max} (film)/cm^{-1} 2935, 2833, 1640, 1598, 1576, 1487, 1453, 1427, 1252, 1217, 1145, 1121, 1096; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.18 (t, *J*=7.8 Hz, 1H, **3**-Ar*H*), 7.05 (d, *J*=13.0 Hz, 1H, CH_3OCH), 6.84–6.83 (m, 1H, **2**-Ar*H*), 6.77–6.76 (m, 1H, **1**-Ar*H*), 6.69 (dd, *J*=8.2, 2.0 Hz, 1H, **4**-Ar*H*), 5.78 (d. *J*=13.0 Hz, 1H, CH_3OCHCH), 3.80 (s, 3H, CH_3O(C)), 3.68 (s, 3H, CH_3OCH); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 159.9 (C_q), 149.2 (CH), 137.9 (C_q), 129.7 (CH), 117.8 (CH), 111.2 (CH), 110.8 (CH), 105.0 (CH), 56.6 (CH_3), 55.3 (CH_3); LRMS (EI) 165 (100), 164 (35), 87 (7), 85 (16).

2-Methoxy-6-(2-methoxyvinyl)naphthalene *Z*-126f and *E*-126f



Synthesised using 2-ethynyl-6-methoxynaphthalene, according to general procedure **B**.

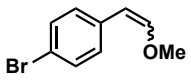
Z:*E* = 52:48. *E* and *Z* isomers were separated *via* column chromatography, 51% combined yield;

***Z*-126f**: colourless oil; ν_{max} (film)/cm^{-1} 2933, 1648, 1602, 1482, 1387, 1265, 1216, 1149, 1087, 1029; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.94 (s, 1H, Ar*H*), 7.69 (t, *J*=8.5 Hz, 2H, Ar*H*), 6.43 (d, *J*=8.7 Hz, 1H, Ar*H*), 7.10–7.08 (m, 2H, Ar*H*), 6.19 (d, *J*=7.0 Hz, 1H, CH_3OCH), 5.34 (d, *J*=7.0 Hz, 1H, CH_3OCHCH), 3.91 (s, 3H, CH_3O(C)), 3.83 (s, 3H, CH_3OCH); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 157.4 (C_q), 147.8 (CH), 133.0 (C_q), 131.5 (C_q), 129.5 (CH), 129.2 (C_q), 127.7 (CH), 126.5 (CH), 126.5 (CH), 118.7 (CH), 105.9 (CH), 105.7 (CH), 60.9 (CH_3), 55.4 (CH_3); LRMS (CI) 215 (100), 200 (10), 183 (7), 171 (8), 128 (3); HRMS (CI) calc'd for $C_{14}H_{15}O_2$ (M+H) requires 215.1072, found 215.1070.

***E*-126f**: Pale cream solid (contaminated with 10% *Z*-isomer); ν_{max} (solid/cm^{-1}) 2930, 2839, 1633, 1599, 1504, 1482, 1448, 1437, 1387, 1266, 1247, 1207, 1166; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.65–7.63 (m, 2H, Ar*H*), 7.53 (s, 1H, Ar*H*), 7.40 (dd, *J*=8.6,

1.8 Hz, 1H, Ar*H*), 7.14 (d, *J*=12.9 Hz, 1H, CH_3OCH), 7.11–7.08 (m, 2H, Ar*H*), 5.95 (d, *J*=12.9 Hz, 1H, CH_3OCHCH), 3.91 (s, 3H, $CH_3O(C)$), 3.72 (s, 3H, CH_3OCH); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 157.2 (C_q), 148.7 (CH), 133.1 (C_q), 131.7 (C_q), 129.4 (C_q), 129.0 (CH), 127.2 (CH), 124.0 (CH), 123.8 (CH), 119.0 (CH), 105.9 (CH), 105.4 (CH), 56.7 (CH_3), 55.4 (CH_3).

1-Bromo-4-(2-methoxyvinyl)benzene *Z*-126g and *E*-126g

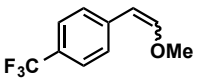


Synthesised using 4-ethynylbromobenzene, according to general procedure **B**.
Z:*E* = 41:59. *E* and *Z* isomers were separated *via* column chromatography, 53% combined yield;

***Z*-126g**: colourless oil; ν_{max} (film)/cm^{-1} 2933, 1649, 1624, 1485, 1453, 1407, 1311, 1289, 1266, 1200, 1088; ^1H NMR (600 MHz, $CDCl_3$) δ_H 7.43 (d, *J*=8.6 Hz, 2H, Br(C)C*H*CH), 7.38 (d, *J*=8.6 Hz, 2H, Br(C)CHC*H*), 6.16 (d, *J*=7.0 Hz, 1H, CH_3OCH), 5.16 (d, *J*=7.0 Hz, 1H, CH_3OCHCH), 3.79 (s, 3H, CH_3O); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 148.7 (CH), 134.9 (C_q), 131.3 (CH), 129.8 (CH), 119.2 (C_q), 104.7 (CH), 60.9 (CH_3); LRMS (EI) 214 (30), 212 (29), 171 (16), 169 (19), 118 (92), 90 (51), 89 (65), 86 (68), 84 (100); HRMS (EI) calc'd for C_9H_9BrO (M^+) requires 211.9837, found 211.9832.

***E*-126g**: Colourless oil (contaminated with 14% *Z*-isomer); ν_{max} (film)/cm^{-1} 2934, 2833, 1700, 1640, 1487, 1462, 1400, 1312, 1291, 1241, 1190; ^1H NMR (600 MHz, $CDCl_3$) δ_H 7.36 (d, *J*=8.5 Hz, 2H, Br(C)CHC*H*), 7.09 (2H, d, *J*=8.5 Hz, 2H, Br(C)C*H*), 7.03 (d, *J*=13.0 Hz, 1H, CH_3OCH), 5.73 (d, *J*=13.0 Hz, 1H, CH_3OCHCH), 3.68 (s, 3H, CH_3O); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 149.4 (CH), 135.5 (C_q), 131.7 (CH), 126.7 (CH), 119.1 (C_q), 104.1 (CH), 56.7 (CH_3); LRMS (EI) 214 (15), 212 (15), 185 (42), 183 (38), 171 (33), 169 (35), 157 (19), 155 (20), 118 (59), 90 (57), 89 (100).

1-(2-Methoxyvinyl)-4-(trifluoromethyl)benzene *Z*-126i and *E*-126i



Synthesised using 1-ethynyl-4-(trifluoromethyl)benzene, according to general procedure **B**.

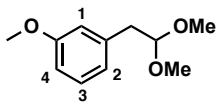
Z:*E* = 30:70. *E* and *Z* isomers were separated *via* column chromatography, 31% combined yield;

***Z*-126i**: pale yellow oil; ν_{max} (film)/cm^{-1} 2924, 2853, 1643, 1614, 1323, 1273, 1186, 1161, 1121, 1095; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.64 (d, *J*=8.1 Hz, 2H, CF_3(C)CHC*H*), 7.51 (d, *J*=8.1 Hz, 2H, CF_3(C)C*H*), 6.24 (d, *J*=6.9 Hz, 1H, CH_3OC*H*), 5.25 (d, *J*=6.9 Hz, 1H, CH_3OCHC*H*), 3.82 (s, 3H, C*H*$_3$O); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 150.0 (CH), 139.5 (C_q), 128.2 (CH), 127.4 (q, *J*=32.1 Hz) (C_q), 125.2 (q, *J*=3.8 Hz) (CH), 124.5 (q, *J*=271.8 Hz) (C_q), 104.5 (CH), 61.1 (CH_3); LRMS (EI) 202 (21), 183 (24), 159 (100), 151 (15), 133 (5), 109 (73).

***E*-126i**: Pale yellow oil (contaminated with 8% *Z*-isomer); ν_{max} (film)/cm^{-1} 2926, 2854, 1728, 1657, 1642, 1615, 1413, 1324, 1163, 1123; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.50 (d, *J*=8.2 Hz, 2H, CF_3(C)CHC*H*), 7.30 (d, *J*=8.2 Hz, 2H, CF_3(C)C*H*), 7.14 (d, *J*=13.0 Hz, 1H, CH_3OC*H*), 5.81 (d, *J*=13.0 Hz, 1H, CH_3OCHC*H*), 3.72 (s, 3H, C*H*$_3$O); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 150.7 (CH), 140.3 (C_q), 127.5 (q, *J*=33.0 Hz) (C_q), 125.7 (q, *J*=3.8 Hz) (CH), 125.1 (CH), 124.6 (q, *J*=271.3 Hz) (C_q), 104 (CH), 56.8 (CH_3); LRMS (EI) 202 (100), 183 (10), 173 (34), 159 (72), 151 (5), 145 (12), 109 (14).

Data in agreement with literature values.[o]

1-(2,2-Dimethoxyethyl)-3-methoxybenzene 131e

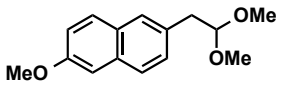


Synthesised using 3-ethynylanisole, according to general procedure **B**.

Colourless oil, 28%; ν_{max} (film)/cm^{-1} 2934, 2829, 1600, 1583, 1488, 1452, 1435, 1361, 1309, 1292, 1257, 1229, 1116, 1041; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.21 (t, *J*=7.8 Hz,

1H, **3**-Ar*H*), 6.84–6.76 (m, 3H, **1**,**2**,**4**-Ar*H*), 4.55 (t, *J*=5.6 Hz, 1H, CH_3OCH), 3.80 (s, 3H, $CH_3O(C)$), 3.34 (s, 6H, 2 x CH_3O), 2.89 (d, *J*=5.6 Hz, 2H, $ArCH_2$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 159.6 (C_q), 138.7 (C_q), 129.4 (CH), 121.9 (CH), 115.3 (CH), 111.8 (CH), 105.3 (CH), 55.3 (CH_3), 53.5 (CH_3), 39.8 (CH_2); LRMS (EI) 196 (4), 165(18), 135 (3), 121 (9), 75 (100); HRMS (EI) calc'd for $C_{11}H_{16}O_3$ (M^+) requires 196.1099, found 196.1099.

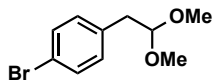
2-(2,2-Dimethoxyethyl)-6-methoxynaphthalene 131f



Synthesised using 2-ethynyl-6-methoxynaphthalene, according to general procedure **B**.

White solid, 21%; MP=57–58 °C; ν_{max} (film)/cm^{-1} 2957, 2937, 2903, 2834, 1632, 1601, 1483, 1460, 1390, 1260, 1232, 1183, 1117, 1047; ^1H NMR (600 MHz, $CDCl_3$) δ_H 7.69 (t, *J*=8.0 Hz, 2H), 7.62 (s, 1H), 7.35 (dd, *J*=8.4, 1.6 Hz, 1H), 7.14–7.12 (m, 2H), 4.62 (t, *J*=5.7 Hz, 1H), 3.92 (s, 3H), 3.37 (s, 6H), 3.05 (d, *J*=5.7 Hz, 2H); ^{13}C NMR 157.4 (C_q), 133.4 (C_q), 132.3 (C_q), 129.2 (CH), 129.1 (C_q), 128.5 (CH), 127.8 (CH), 126.8 (CH), 118.9 (CH), 105.7 (CH), 105.6 (CH), 55.4 (CH_3), 53.6 (CH_3), 39.8 (CH_2); HRMS (ESI) calc'd for $C_{15}H_{18}ONa$ (M+Na) requires 269.1154, found 269.1153.

1-Bromo-4-(2,2-dimethoxyethyl)benzene 131g

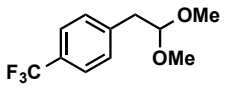


Synthesised using 4-ethynylbromobenzene, according to general procedure **B**.

Colourless oil, 14%; ν_{max} (film)/cm^{-1} 2932, 2830, 1488, 1362, 1189, 1118, 1071, 1043, 1011; ^1H NMR (600 MHz, $CDCl_3$) δ_H 7.41 (d, *J*=8.3 Hz, 2H, Br(C)C*H*), 7.11 (d, *J*=8.3 Hz, 2H, Br(C)CHC*H*), 4.49 (t, *J*=5.6 Hz, 1H, CH_3OCH), 3.33 (s, 6H, 2×CH_3O), 2.86 (d, *J*=5.6 Hz, 2H, $ArCH_2$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 136.1 (C_q), 131.5 (CH), 131.3 (CH), 120.7 (C_q), 105.1 (CH), 53.6 (CH_3), 39.2 (CH_2); LRMS (EI) 245

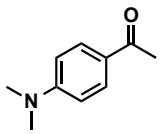
(1), 243 (1), 171 (44), 169 (46), 134 (100), 118 (19); HRMS (EI) calc'd for $C_{10}H_{13}BrO_2$ (M^+) requires 244.0098, found 244.0092.
Data in agreement with literature values.[r]

1-(2,2-Dimethoxyethyl)-4-(trifluoromethyl)benzene 131i



Synthesised using 1-ethynyl-4-(trifluoromethyl)benzene, according to general procedure **B**.
Colourless oil, 32%; ν_{max} (film)/cm^{-1} 2935, 2831, 1618, 1438, 1417, 1363, 1321, 1228, 1161, 1107, 1063; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.55 (d, *J*=8.0 Hz, 2H, CF_3(C)C*H*), 7.35 (d, *J*=8.0 Hz, 2H, CF_3(C)CHC*H*), 4.54 (t, *J*=5.6 Hz, 1H, C*H*(OCH_3)$_2$), 3.35 (s, 6H, 2×OCH_3), 2.96 (d, *J*=5.6 Hz, 2H, CHC*H*$_2$Ar); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 141.2 (C_q), 129.9 (CH), 128.8 (q, *J*=32.3 Hz) (C_q), 125.3 (q, *J*=3.8 Hz) (CH), 123.5 (q, *J*=273.8 Hz) (C_q), 104.9 (CH), 53.6 (CH_3), 39.6 (CH_2); LRMS (CI) Mass ion not observed, 220 (8), 205 (30), 188 (100), 75 (31).

1-(4-(Dimethylamino)phenyl)ethan-1-one 132b

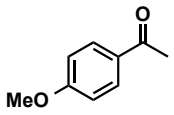


Synthesised using 4-ethynyl-*N*,*N*-dimethylaniline, according to general procedure **B**.
White film, 7%; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.88 (d, *J*=9.0 Hz, 2H, N(C)CHC*H*), 6.66 (d, *J*=9.0 Hz, 2H, N(C)C*H*), 3.07 (s, 6H, (CH_3)$_2$N), 2.52 (s, 3H, C*H*$_3$(C)); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 196.6 (C_q), 153.5 (C_q), 130.7 (CH), 125.4 (C_q), 110.7 (CH), 40.2 (CH_3), 26.2 (CH_3); HRMS (ESI) calc'd for $C_{10}H_{14}NO$ (M+H) requires 164.1075, found 164.1076. Data in agreement with literature values.[s]

[r] Fañanás, F. J.; Álvarez-Pérez, M.; Rodriguez, F., *Chem. Eur. J.*, **2005**, *11*, 5938

[s] Bassetti, M.; Ciceri, S.; Lancia, F.; Pasquini, C., *Tetrahedron Lett.*, **2014**, *55*, 1608

1-(4-Methoxyphenyl)ethan-1-one 132c



Synthesised using 4-ethynylanisole, according to general procedure **B**.

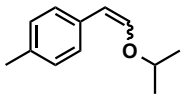
Colourless oil, 7%; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.95 (d, *J*=8.8 Hz, 2H, O(C)CHC*H*), 6.94 (d, *J*=8.8 Hz, 2H, O(C)C*H*), 3.88 (s, 3H, CH_3O), 2.57 (s, 3H, CH_3(C)); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 197.0 (C_q), 163.6 (C_q), 130.7 (CH), 130.4 (C_q), 113.8 (CH), 55.6 (CH_3), 26.5 (CH_3); LRMS (EI) 150 (34), 135 (100), 121 (5), 107 (11), 92 (23).

Data in agreement with literature values.[r]

General Procedure C: Synthesis of 136 and 137

To a flame dried flask under an atmosphere of argon was added alcohol (isopropanol or benzyl alcohol, 0.96 mmol, 4.0 eq), followed by anhydrous THF (1.0 mL). Potassium hydride (38 mg, 0.96 mmol, 4.0 eq, washed with PE and dried between filter paper immediately prior to use) was added to the solution as a single portion, giving a white paste. The mixture was stirred at rt for 10 min, then gently warmed to 50 °C for 20 min. Upon cooling to rt, THF was removed *in vacuo*, and the resulting solid dissolved in anhydrous DMF (1.5 mL). To the solution was added DMEDA (52 μL, 0.48 mmol, 2.0 eq) and *p*-tolylacetylene (30 μL, 0.24 mmol, 1.0 eq) as a single burst. The solution was stirred at 55 °C until complete conversion of *p*-tolylacetylene was observed (3 h). Residual potassium salts were quenched by addition of *i*PrOH (1 mL), and the crude mixture was diluted with CH_2Cl_2 (100 mL). The organic portion was washed with 2.0 M LiCl solution (3 x 20 mL), then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification *via* column chromatography (0–5% EtOAc/PE) yielded **136** and **137**.

1-(2-Isopropoxyvinyl)-4-methylbenzene *Z*-136 and *E*-136



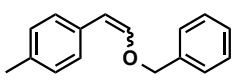
Synthesised using 4-ethynyltoluene, according to General Procedure **C**.

Z:*E* = 60:40. *E* and *Z* isomers were separated *via* column chromatography, 43% combined yield;

***Z*-136**: Pale yellow oil; ν_{max} (film)/cm^{-1} 2974, 1648, 1511, 1453, 1422, 1383, 1372, 1338, 1259, 1117, 1074; ^{1}H NMR (600 MHz, CD_2Cl_2) δ_H 7.45 (d, *J*=8.0 Hz, 2H, CH_3(C)CHC*H*), 7.07 (d, *J*=8.0 Hz, 2H, CH_3(C)C*H*), 6.22 (d, *J*=7.0 Hz, 1H, OC*H*CH), 5.16 (d, *J*=7.0 Hz, 1H, OCHC*H*), 4.05 (quintet, *J*=6.3 Hz, 1H, OC*H*(CH_3)$_2$), 2.29 (s, 3H, CH_3(C)), 1.31 (d, *J*=6.3 Hz, 6H, CH(C*H*$_3$)$_2$); ^{13}C NMR (150 MHz, CD_2Cl_2) δ_C 144.9 (CH), 135.0 (C_q), 133.5 (C_q), 128.7 (CH), 127.9 (CH), 104.9 (CH), 75.8 (CH), 22.3 (CH_3), 20.1 (CH_3); LRMS (EI) 176 (43), 134 (100), 119 (48), 105 (76), 91 (20); HRMS (EI) calc'd for $C_{12}H_{16}O$ (M^+) requires 176.1201, found 176.1206.

***E*-136**: Colourless oil; ν_{max} (film)/cm^{-1} 2974, 1654, 1635, 1513, 1384, 1372, 1317, 1218, 1177, 1151, 1111; ^{1}H NMR (600 MHz, CD_2Cl_2) δ_H 7.10 (d, *J*=8.0 Hz, 2H, CH_3(C)CHC*H*), 7.05 (d, *J*=8.0 Hz, 2H, CH_3(C)C*H*), 6.84 (d, *J*=12.7 Hz, 1H, OC*H*CH), 5.83 (d, *J*=12.7 Hz, 1H, OCHC*H*), 4.11 (quintet, *J*=6.2 Hz, 1H, OC*H*(CH_3)$_2$), 2.28 (s, 3H, C*H*$_3$(C)), 1.26 (d, *J*=6.2 Hz, 6H, CH(C*H*$_3$)$_2$); ^{13}C NMR (150 MHz, CD_2Cl_2) δ_C 146.2 (CH), 135.1 (C_q), 133.7 (C_q), 129.1 (CH), 124.7 (CH), 107.0 (CH), 73.6 (CH), 22.1 (CH_3), 20.7 (CH_3); LRMS (EI) 176 (9), 134 (25), 105 (16), 85 (63), 83 (100); HRMS (EI) calc'd for $C_{12}H_{16}O$ (M^+) requires 176.1201, found 176.1204.

(2-(Benzyloxy)vinyl)benzene *Z*-137 and *E*-137



Synthesised using 4-ethynyltoluene, according to General Procedure **C**.

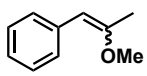
Z:*E* = 40:60. *E* and *Z* isomers were separated *via* column chromatography, 61% combined yield;

***Z*-137**: Pale yellow oil; ν_{max} (film)/cm^{-1} 3029, 2921, 2859, 1649, 1512, 1453, 1419, 1367, 1299, 1261, 1198, 1086, 1074; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.53 (d, *J*=7.9 Hz, 2H, $CH_3(C)CHCH$), 7.40–7.36 (m, 4H, *o*- and *m*- Ar*H*), 7.33–7.31 (m, 1H, *p*-Ar*H*), 7.11 (d, *J*=7.9 Hz, 2H, $CH_3(C)CH$), 6.23 (d, *J*=7.0 Hz, 1H, OC*H*CH), 5.25 (d, *J*=7.0 Hz, 1H, OCHC*H*), 4.99 (s, 2H, OCH_2Ph), 2.32 (s, 3H, $CH_3(C)$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 145.7 (CH), 137.5 (C_q), 135.5 (C_q), 133.1 (C_q), 129.0 (CH), 128.7 (CH), 128.3 (CH), 128.1 (CH), 127.3 (CH), 106.3 (CH), 74.9 (CH_2), 21.3 (CH_3); LRMS (CI) 225 (29), 224 (32), 207 (32), 195 (10), 147 (6), 133 (8), 119 (8), 105 (46), 91 (100); HRMS (CI) calc'd for $C_{16}H_{17}O$ ($M+H^+$) requires 225.1279, found 225.1274.

***E*-137**: Pale yellow oil (contaminated with 15% *Z*-isomer); ν_{max} (film)/cm^{-1} 3033, 3017, 2913, 2870, 1636, 1512, 1453, 1377, 1319, 1224, 1213, 1150, 1104, 1080; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.40–7.37 (m, 4H, *o*- and *m*-Ar*H*), 7.34–7.32 (m, 1H, *p*-Ar*H*), 7.13 (d, *J*=8.0 Hz, 2H, $CH_3(C)CHCH$), 7.07 (d, *J*=8.0 Hz, 2H, $CH_3(C)CH$), 7.04 (d, *J*=13.0 Hz, 1H, OC*H*CH), 5.95 (d, *J*=13.0 Hz, 1H, OCHC*H*), 4.89 (s, 2H, OCH_2Ph), 2.31 (s, 3H, $CH_3(C)$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 147.2 (CH), 136.9 (C_q), 135.5 (C_q), 133.4 (C_q), 129.4 (CH), 128.7 (CH), 128.2 (CH), 127.7 (CH), 125.2 (CH), 106.9 (CH), 71.9 (CH_2), 21.2 (CH_3); LRMS (CI) 225 (14), 224 (15), 207 (21), 173 (5), 125 (5), 111 (33), 105 (40), 97 (31), 91 (100).

Data in agreement with literature values.[t]

(2-Methoxyprop-1-en-1-yl)benzene *Z*-139 and *E*-139



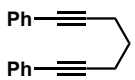
Synthesised according to General Procedure **B**, using prop-1-yn-1-ylbenzene in place of terminal alkynes.

E and *Z* isomers could not be separated *via* column chromatography, and data was obtained from a mixture.

[t] Alcaide, B.; Pérez-Castells, J.; Polance, C.; Sierra, M. A., *J. Org. Chem.*, **1995**, *60*, 6012

Colourless oil, 51% combined yield; ***Z*-139**; ^{1}H NMR (600 MHz, CD_2Cl_2) δ_H 7.28 (t, *J*=7.7 Hz, 2H, *o*-Ar*H*), 7.19 (d, 2H, *J*=7.5 Hz, *m*-Ar*H*), 7.12 (t, *J*=7.4 Hz, 1H, *p*-Ar*H*), 5.60 (s, 1H, ArC*H*), 3.64 (s, 3H, CH_3O), 1.98 (s, 3H, CH_3(C)); ^{13}C NMR (150 MHz, CD_2Cl_2) δ_C 156.4 (C_q), 137.9 (C_q), 128.6 (CH), 128.1 (CH), 124.9 (CH), 99.3 (CH), 54.5 (CH_3), 17.7 (CH_3); ***E*-139**; ^{1}H NMR (600 MHz, CD_2Cl_2) δ_H 7.50 (d, *J*=7.4 Hz, 2H, *o*-Ar*H*), 7.23 (t, *J*=7.6 Hz, 2H, *m*-Ar*H*), 7.07 (t, *J*=7.4 Hz, 1H, *p*-Ar*H*), 5.29 (s, 1H, ArC*H*), 3.72 (s, 3H, CH_3O), 2.05 (s, 3H, CH_3(C)); ^{13}C NMR (150 MHz, CD_2Cl_2) δ_C 153.8 (C_q), 136.9 (C_q), 127.9 (CH), 127.7 (CH), 124.9 (CH), 105.8 (CH), 54.9 (CH_3), 18.3 (CH_3); LRMS (CI) 149 (100), 117 (24), 105 (4).
Data in agreement with literature values.[u]

1,7-Diphenylhepta-1,6-diyne 140



In a flame dried flask under an atmosphere of argon, $Pd(PPh_3)_4$ (12 mg, 0.01 mmol, 0.5 mol%), CuI (4 mg, 0.02 mmol, 1.0 mol%) and iodobenzene (1.22 g, 6.0 mmol, 3.0 eq) were mixed with degassed di*iso*propylamine (20 mL). 1,6-Heptadiyne (184 mg, 2.0 mmol, 1.0 eq) was dissolved in degassed di*iso*propylamine (5 mL), and added to the solution dropwise over a period of 5 min. The resulting solution was stirred at rt for 18 h, then filtered through Celite® and washed with Et_2O (50 mL). The solvent was removed *in vacuo*, and the crude product purified *via* column chromatography (0–10% CH_2Cl_2/PE) to yield **140**.

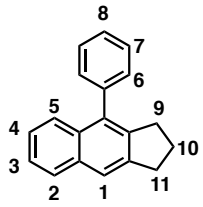
Pale yellow oil, 71%; ν_{max} (film)/cm^{-1} 3078, 3054, 2935, 2902, 2864, 2835, 2230, 1597, 1489, 1441, 1429, 1343, 1329; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.42–7.41 (m, 4H, 2 x *o*-Ar*H*), 7.31–7.28 (m, 6H, 2 x *m*- and *p*-Ar*H*), 2.61 (t, *J* = 7.1 Hz, 4H, 2 x (C)CH_2), 1.92 (pent., *J* = 7.1 Hz, 2H, $CH_2CH_2CH_2$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 131.7 (CH), 128.3 (CH), 127.8 (CH), 123.9 (C_q), 89.3 (C_q), 81.3 (C_q), 28.1 (CH_2), 18.8 (CH_2); LRMS (EI) 244 (68), 228 (70), 215 (46), 202 (17), 178 (5), 167 (39), 152 (11),

[u] Gronheid, R.; Lodder, G.; Ochiai, M.; Sueda, T.; Okuyama, T., *J. Am. Chem. Soc.*, **2001**, *123*, 8760

128 (19), 115 (28); HRMS (EI) calc'd for $C_{19}H_{16}$ (M^+) requires 244.1247, found 244.1249.

Data in agreement with literature values.[v]

4-Phenyl-2,3-dihydro-1*H*-cyclopenta[*b*]naphthalene 145



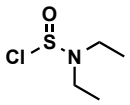
In a flame-dried sealed tube charged with a stirrer bar and under an argon atmosphere, KOMe (29 mg, 0.41 mmol, 2.0 eq) was diluted with DMF (spiked with 1% MeOH, 1.5 mL). The reaction flask was cooled to 0 °C, and 1,7-diphenylhepta-1,6-diyne (**140**) was added as a single portion *via* syringe. The mixture was gently warmed to 80 °C and stirred for 2 h. With a new product visible *via* TLC, the reaction was quenched by addition of water (1 mL), and diluted with CH_2Cl_2 (20 mL). The organic portion was washed with saturated LiCl solution (3 x 10 mL), and solvent removed *in vacuo*. The crude material was redissolved in Et_2O (20 mL) and washed with saturated sodium chloride solution (10 mL). The organic portion was dried over $MgSO_4$, filtered, concentrated, and purified *via* column chromatography (0–2% EtOAc/PE).

Colourless oil, 20%; ν_{max} (film)/cm^{-1} 3056, 2948, 1600, 1493, 1027, 850; ^{1}H NMR (600 MHZ, $CDCl_3$) δ_H 7.82 (d, J = 8.2 Hz, 1H, **5**-Ar*H*), 7.70 (s, 1H, **1**-Ar*H*), 7.58 (d, J = 8.5 Hz, 1H, **2**-Ar*H*), 7.50 (t, J = 7.3 Hz, 2H, **7**-Ar*H*), 7.43–7.36 (m, 4H, **3**-, **6**- and **8**-Ar*H*), 7.30 (t, J = 7.6 Hz, 1H, **4**-Ar*H*), 3.13 (td, J = 7.5, 1.0 Hz, 2H, **11**-CH_2), 2.83 (t, J = 7.3 Hz, 2H, **9**-CH_2), 2.09 (quint, J = 7.4 Hz, 2H, **10**-CH_2); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 143.0 (C_q), 141.8 (C_q), 139.6 (C_q), 134.7 (C_q), 133.3 (C_q), 131.6 (C_q), 130.1 (CH), 128.4 (CH), 127.7 (CH), 127.1 (CH), 125.9 (CH), 125.0 (CH), 124.9 (CH), 121.9 (CH), 33.2 (CH_2), 32.6 (CH_2), 26.1 (CH_2); HRMS (EI) calc'd for $C_{19}H_{16}$ (M^+) requires 244.1247, found 244.1251.

[v] Lucht, B. L.; Mao, S. S. H.; Tilley, T. D., *J. Am. Chem. Soc.*, **1988**, *120*, 4354

Data in agreement with literature values.[w]

Diethylsulfuramidous chloride



A flame-dried, 500 mL flask under an atmosphere of argon was charged with a stirrer bar, thionyl chloride (9.52 g, 80.0 mmol, 1.0 eq) and anhydrous Et_2O (150 mL). The solution was cooled to –40 °C, and *N*,*N*-diethylamine (11.5 g, 160.0 mmol, 2.0 eq) dissolved in anhydrous Et_2O (100 mL) was added dropwise *via* syringe pump over a period of 2 h. Following addition, the solution was allowed to gently warm to –10 °C, and stirred for a further 1 h. The crude reaction mixture was warmed to rt, then filtered through a pad of Celite® and washed with Et_2O. The organic solvent was removed *in vacuo*, taking care to avoid complete dryness. The lumpy, brown oil was stored under argon at –20 °C between use.

Brown oil, 45%; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 3.42 (m, 4H, 2 x NC*H*$_2$CH$_3$), 1.30 (m, 6H, 2 x NCH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 39.2 (CH_2), 12.3 (CH_3); LRMS (EI) Mass ion not detected.
Data in agreement with literature values.[x]

General Procedure D: Synthesis of alkynyl sulfinamides 152–160

To a flame-dried flask under an atmosphere of argon was transferred anhydrous THF (20 mL) and acetylene (1.38–3.87 mmol, 1.1 eq). The solution was cooled to –78 °C, then ^{n}BuLi[y] (1.6 M in hexanes, 1.1 eq) was added dropwise *via* syringe. The mixture was stirred at –78 °C for 10 min, before diethylsulfuramidous chloride (1.0 eq) was added dropwise over 30 s. The solution was stirred at –78 °C for a further 20 min,

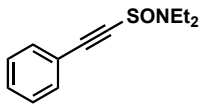
[w] Lin, G. -Y.; Yang, C. -Y.; Liu, R. -S., *J. Org. Chem.*, **2007**, *72*, 6753

[x] Gupta, S. K., *Synthesis*, **1977**, 39

[y] KHMDS (0.5 M in toluene, 1.1 eq) was used in place of ^{n}BuLi in the synthesis of **154** and **157**

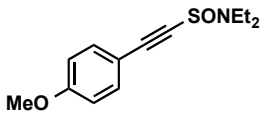
before being allowed to warm to rt. The crude mixture was diluted with CH_2Cl_2 (200 mL) and washed with water (100 mL) and saturated sodium chloride solution (100 mL). The organic portion was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified *via* column chromatography (0–20% EtOAc/PE) to yield sulfinamides **152–160**.

N,*N*-Diethyl-2-phenylethynesulfinamide 152



Synthesised using phenylacetylene, according to general procedure **D**.
Colourless oil, 51%; ν_{max} (film)/cm^{-1} 2978, 2165, 1725, 1491, 1182, 1091; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.51 (d, J = 7.7 Hz, 2H, *o*-Ar*H*), 7.42 (m, 1H, *p*-Ar*H*), 7.36 (m, 2H, *m*-Ar*H*), 3.42 (dq, J = 14.2, 7.1 Hz, 2H, 2 x NC*H*), 3.37 (dq, J = 14.2, 7.1 Hz, 2H, 2 x NC*H*), 1.28 (t, J = 7.1 Hz, 6H, 2 x NCH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 132.2 (CH), 130.3 (CH), 128.6 (CH), 120.2 (C_q), 96.4 (C_q), 86.5 (C_q), 42.7 (CH_2), 14.3 (CH_3). LRMS (EI) 221 (3), 205 (3), 202 (20), 173 (100), 158 (37), 149 (76).
Data in agreement with literature values.[z]

N,*N*-Diethyl-2-(4-methoxyphenyl)ethynesulfinamide 153



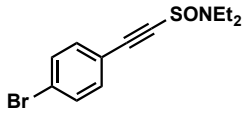
Synthesised using 4-ethynylanisole, according to general procedure **D**.
Pale yellow oil, 72%; ν_{max} (film)/cm^{-1} 2973, 2157, 1602, 1507, 1460, 1251, 1171, 1088; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.45 (d, J = 9.0 Hz, 2H, 2 x $CH_3O(C)CHCH$), 6.87 (d, J = 9.0 Hz, 2H, 2 x $CH_3O(C)CH$), 3.83 (s, 3H, CH_3O), 3.41 (dq, J = 7.2, 14.0 Hz, 2H, 2 x NC*H*), 3.36 (dq, J = 7.2, 14.0 Hz, 2H, 2 x NC*H*), 1.28 (t, J = 7.6 Hz, 6H, 2 x NCH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 161.2 (C_q), 133.9 (CH), 114.3 (CH),

[z] Gray, V. J.; Slater, B.; Wilden, J. D., *Chem. Eur. J.*, **2012**, *18*, 15582

112.1 (C_q), 97.2 (C_q), 85.3 (C_q), 55.5 (CH_3), 42.6 (CH_2), 14.3 (CH_3). LRMS (CI) 252 (30), 235 (26), 203 (100), 179 (45).

Data in agreement with literature values.[z]

_N_,_N_-Diethyl-2-(4-bromophenyl)ethynesulfinamide 154

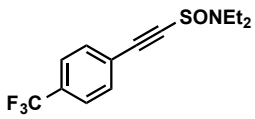


Synthesised using 4-ethynylbromobenzene, according to general procedure **D**.

Pale yellow oil, 86%; ν_{max} (film)/cm^{-1} 2925, 2854, 2169, 1585, 1484, 1215, 1070, 1010; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.51 (d, J = 8.5 Hz, 2H, 2 x Br(C)C*H*CH), 7.37 (d, J = 8.5 Hz, 2H, 2 x Br(C)CHC*H*), 3.42 (dq, J = 14.3, 7.1 Hz, 2H, 2 x NC*H*), 3.37 (dq, J = 14.3, 7.1 Hz, 2H, 2 x NC*H*), 1.28 (t, J = 7.1 Hz, 6H, 2 x NCH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 133.5 (CH), 132.1 (CH), 125.0 (C_q), 119.1 (C_q), 95.2 (C_q), 87.6 (C_q), 42.8 (CH_2), 14.4 (CH_3); LRMS (CI) 302 (21), 300 (21), 285 (10), 283 (10), 253 (86), 251 (85), 238 (12); HRMS (CI) calc'd for $C_{12}H_{15}BrNOS$ $(M+H)^+$ 300.0052, found 300.0050.

Data in agreement with literature values.[z]

_N_,_N_-Diethyl-2-(4-trifluoromethylphenyl)ethynesulfinamide 155

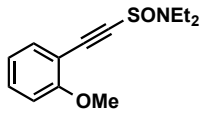


Synthesised using 1-ethynyl-4-(trifluoromethyl)benzene, according to general procedure **D**.

Yellow oil, 45%; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.63 (s, 4H, 4 x Ar*H*), 3.41 (dq, J = 14.1, 7.3 Hz, 2H, 2 x NC*H*), 3.39 (dq, J = 14.1, 7.3 Hz, 2H, 2 x NC*H*), 1.29 (t, J = 7.3 Hz, 6H, 2 x NCH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 132.5 (CH), 131.8 (q, J = 32.0 Hz) (C_q),125.6 (q, J = 3.3 Hz) (C_q), 124.0 (CH), 122.8 (q, J = 272.0 Hz) (C_q), 94.2 (C_q), 88.7 (C_q), 42.8 (CH_2), 14.4 (CH_3). LRMS (CI) 290 (4), 273 (4), 241 (25), 173 (8), 84 (100).

Data in agreement with literature values.[z]

***N*,*N*-Diethyl-2-(2-methoxyphenyl)ethynesulfinamide 156**

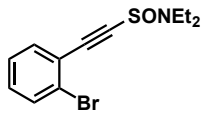


Synthesised using 2-ethynylanisole, according to general procedure **D**.

Pale yellow oil, 91%; ν_{max} (film)/cm^{-1} 2973, 2162, 1595, 1490, 1462, 1381, 1283, 1257, 1180, 1085, 1019; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.46 (dd, J = 7.5, 1.8 Hz, 1H, $CH_3O(C)(C)CH$), 7.38 (t, J = 7.8 Hz, 1H, $CH_3O(C)CHCH$), 6.93 (t, J = 7.5 Hz, 1H, $CH_3O(C)CHCHCH$), 6.89 (d, J = 8.6 Hz, 1H, $CH_3O(C)CH$), 3.87 (s, 3H, CH_3O), 3.45 (dq, J = 14.3, 7.1 Hz, 2H, 2 x NCH_2CH_3), 3.36 (dq, J = 14.3, 7.1 Hz, 2H, 2 x NCH_2CH_3), 1.29 (t, J = 7.1 Hz, 6H, 2 x NCH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 160.9 (C_q), 134.0 (CH), 131.9 (CH), 120.6 (CH), 110.8 (CH), 109.5 (C_q), 93.3 (C_q), 90.2 (C_q), 55.8 (CH_3), 42.6 (CH_2), 14.3 (CH_3). LRMS (CI) 262 (100), 252 (18), 235 (17), 203 (93), 179 (32).

Data in agreement with literature values.[z]

***N*,*N*-Diethyl-2-(2-bromophenyl)ethynesulfinamide 157**

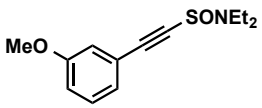


Synthesised using 2-ethynylbromobenzene, according to general procedure **D**.

Yellow oil, 79%; ν_{max} (film)/cm^{-1} 2974, 2934, 2871, 2170, 1464, 1381, 1181, 1091, 1045, 1027, 1008; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.61 (d, J = 8.0 Hz, 1H, Br(C)C*H*), 7.55 (dd, J = 7.7, 1.4 Hz, 1H, Br(C)(C)C*H*), 7.34–7.23 (m, 2H, Br(C)CHC*H* and Br(C)CHCHC*H*), 3.44 (dq, J = 14.0, 7.1 Hz, 2H, 2 x NC*H*), 3.41 (dq, J = 14.0, 7.1 Hz, 2H, 2 x NC*H*), 1.29 (t, J = 7.2 Hz, 6H, 2 x NCH_2CH_3) ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 134.3 (CH), 132.8 (CH), 131.4 (CH), 127.4 (CH), 125.9 (C_q), 122.7 (C_q), 94.0 (C_q), 90.5 (C_q), 42.7 (CH_2), 14.4 (CH_3); LRMS (CI) 302 (9), 300 (9), 285 (14),

283 (14), 253 (98), 251 (100), 238 (17), 236 (18), 229 (13), 227 (12), 120 (29); HRMS (CI) calc'd for $C_{12}H_{15}BrNOS$ $(M+H)^+$ 300.0052, found 300.0039.

N,*N*-Diethyl-2-(3-methoxyphenyl)ethynesulfinamide 158

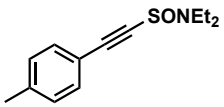


Synthesised using 3-ethynylanisole, according to general procedure **D**.

Yellow oil, 65%; ν_{max} (film)/cm^{-1} 2974, 2159, 1574, 1462, 1286, 1156, 1089; ^1H NMR (600 MHz, $CDCl_3$) δ_H 7.27 (t, J = 8.0 Hz, 1H, $CH_3O(C)CHCH$), 7.11 (d, J = 7.7 Hz, 1H, $CH_3O(C)CHCHCH$), 7.03 (m, 1H, $CH_3O(C)CH(C)$), 6.97 (dd, J = 8.0, 2.7 Hz, 1H, $CH_3O(C)CH$), 3.81 (s, 3H, CH_3O), 3.43 (dq, J = 7.3, 14.2 Hz, 2H, 2 x NCH), 3.38 (dq, J = 7.3, 14.2 Hz, 2H, 2 x NCH), 1.28 (t, J = 7.2 Hz, 6H, 2 x NCH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 159.4 (C_q), 129.8 (CH), 124.7 (CH), 121.1 (C_q), 117.0 (CH), 116.8 (CH), 96.3 (C_q), 86.2 (C_q), 55.5 (CH_3), 42.7 (CH_2), 14.4 (CH_3); LRMS (CI) 252 (57), 235 (18), 203 (100), 179 (12), 120 (27).

Data in agreement with literature values.[z]

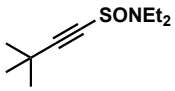
N,*N*-Diethyl-2-(4-methylphenyl)ethynesulfinamide 159



Synthesised using 4-ethynyltoluene, according to general procedure **D**.

Pale yellow oil, 79%; ν_{max} (film)/cm^{-1} 2973, 2934, 2871, 2162, 1604, 1507, 1453, 1380, 1179, 1090; ^1H NMR (600 MHz, $CDCl_3$) δ_H 7.41 (d, J = 7.8 Hz, 2H, $CH_3(C)CHCH$), 7.17 (d, J = 7.8 Hz, 2H, $CH_3(C)CH$), 3.42 (dq, J = 14.2, 7.2 Hz, 2H, 2 x NCH), 3.37 (dq, J = 14.2, 7.2 Hz, 2H, 2 x NCH), 2.37 (s, 3H, $CH_3(C)$), 1.28 (t, J = 7.2 Hz, 6H, 2 x NCH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 140.9 (C_q), 132.2 (CH), 129.4 (CH), 117.1 (C_q), 97.0 (C_q), 85.9 (C_q), 42.7 (CH_2), 21.8 (CH_3), 14.4 (CH_3); LRMS (CI) 236 (12), 219 (16), 187 (100), 172 (12), 163 (20), 148 (6), 120 (14); HRMS (CI) calc'd for $C_{13}H_{18}NOS$ $(M+H)^+$ 236.1104, found 236.1105.

***N*,*N*-Diethyl-2-*tert*butylethynesulfinamide 160**

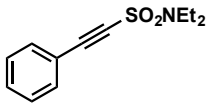


Synthesised using 3,3-dimethyl-1-butyne, according to general procedure **D**.
Pale yellow oil, 92%; ν_{max} (film)/cm^{-1} 2965, 2156, 1636, 1461, 1363, 1252, 1128; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.35 (apparent sextet, J = 7.2 Hz, 4H, 2 x NCH_2CH$_3$), 1.27 (s, 9H, (C)(CH_3)$_3$), 1.23 (t, J = 7.2 Hz, 6H, 2 x NCH$_2$CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 106.4 (C_q), 77.0 (C_q), 42.4 (CH_2), 30.1 (CH_3), 28.2 (C_q), 14.2 (CH_3); LRMS (EI) 202 (12), 120 (14), 58 (100).
Data in agreement with literature values.[z]

General Procedure E: Synthesis of alkynyl sulfonamides 161–169

Sodium metaperiodate (1.99–3.19 mmol, 1.3 eq) was dissolved (with vigorous stirring) in H_2O (4 mL). To the solution was added MeCN (5 mL), and the solution was cooled to 0 °C. Ensuring complete dissolution of $NaIO_4$, EtOAc (5 mL) was added to the mixture, which was stirred for a further 5 min at 0 °C. $RuCl_3.3H_2O$ (0.01 eq) was added, and the solution stirred for a further 2 min. Sulfinamide **152–160** (1.53–2.45 mmol, 1.0 eq), dissolved in EtOAc (5 mL), was added as a single burst. The reaction mixture was stirred vigorously at 0 °C until TLC analysis indicated full starting material conversion (4–5 h). The crude reaction mixture was diluted with CH_2Cl_2 (200 mL) and washed with H_2O (100 mL) and saturated sodium chloride solution (100 mL). The organic portions were combined and dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification *via* column chromatography (0–20% EtOAc/PE) yielded sulfonamides **161–169**.

***N*,*N*-Diethyl-2-phenylethynesulfonamide 161**

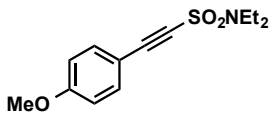


Synthesised using **152**, according to general procedure **E**.

Pale yellow oil, 54%; ν_{max} (film)/cm^{-1} 2978, 2939, 2877, 2181, 1356, 1152, 1016; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.53 (d, J = 7.6 Hz, 2H, *o*-Ar*H*), 7.47 (t, J = 7.6 Hz, 1H, *p*-Ar*H*), 7.39 (t, J = 7.6 Hz, 2H, *m*- Ar*H*), 3.39 (q, J = 7.2 Hz, 4H, 2 x NCH_2), 1.29 (t, J = 7.2 Hz, 6H, 2 x NCH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 132.8 (CH), 131.1 (CH), 128.8 (CH), 118.7 (C_q), 88.3 (C_q), 83.9 (C_q), 43.0 (CH_2), 13.5 (CH_3); LRMS (EI) 237 (10), 222 (95), 173 (49), 165 (100).

Data in agreement with literature values.[z]

***N*,*N*-Diethyl-2-(4-methoxyphenyl)ethynesulfonamide 162**

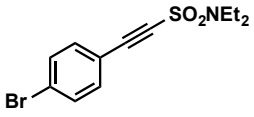


Synthesised using **153**, according to general procedure **E**.

Pale yellow oil, 42%; ν_{max} (film)/cm^{-1} 2977, 2938, 2842, 2175, 1602, 1508, 1355, 1253, 1149, 1017; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.48 (d, J = 8.8 Hz, 2H, 2 x $CH_3O(C)CHCH$), 6.89 (d, J = 8.8 Hz, 2H, 2 x $CH_3O(C)CH$), 3.84 (s, 3H, CH_3O), 3.37 (q, J = 7.2 Hz, 4H, 2 x NCH_2), 1.29 (t, J = 7.2 Hz, 6H, 2 x NCH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 161.8 (C_q), 134.4 (CH), 114.5 (CH), 110.4 (C_q), 89.2 (C_q), 83.0 (C_q), 55.6 (CH_3), 43.0 (CH_2), 13.5 (CH_3). LRMS (EI) 267 (7), 195 (22), 132 (100).

Data in agreement with literature values.[z]

***N*,*N*-Diethyl-2-(4-bromophenyl)ethynesulfonamide 163**

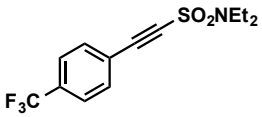


Synthesised using **154**, according to general procedure **E**.

Opaque yellow oil, 59%; ν_{max} (film)/cm^{-1} 2977, 2938, 2875, 2183, 1584, 1485, 1357, 1202, 1153, 1010; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.54 (d, *J* = 8.3 Hz, 2H, Br(C)C*H*), 7.39 (d, *J* = 8.3 Hz, 2H, Br(C)CHC*H*), 3.38 (q, *J* = 7.3 Hz, 4H, 2 x NC*H*$_2$CH$_3$), 1.29 (t, *J* = 7.3 Hz, 2 x NCH$_2$C*H*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 133.9 (CH), 132.2 (CH), 125.9 (C_q), 117.6 (C_q), 86.9 (C_q), 85.0 (C_q), 43.0 (CH_2), 13.5 (CH_3); LRMS (CI) 318 (99), 316 (100), 302 (47), 300 (46), 253 (69), 251 (70), 245 (10), 236 (7), 193 (7); HRMS (CI) calc'd for $C_{12}H_{15}BrNO_2S$ $(M+H)^+$ 316.0001, found 316.0002.

Data in agreement with literature values.[z]

***N*,*N*-Diethyl-2-(4-trifluoromethylphenyl)ethynesulfonamide 164**

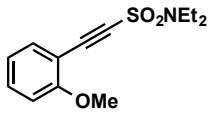


Synthesised using **155**, according to general procedure **E**.

Yellow oil, 43%; ν_{max} (film)/cm^{-1} 2979, 2188, 1724, 1323, 1159, 1129, 1067; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.66 (s, 4H, Ar*H*), 3.40 (q, *J* = 7.2 Hz, 4H, 2 x NC*H*$_2$), 1.30 (t, *J* = 7.2 Hz, 6H, 2 x NCH$_2$C*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 132.9 (CH), 132.6 (q, *J* = 33.0 Hz) (C_q), 125.7 (q, *J* =3.7 Hz) (CH), 123.4 (q, *J* = 272 Hz) (C_q) 122.6 (C_q), 85.9 (C_q), 85.8 (C_q) 43.0 (CH_2), 13.5 (CH_3); LRMS (CI) 306 (100), 290 (60), 241 (40), 233 (17); HRMS (CI) calc'd for $C_{13}H_{15}F_3NO_2S$ $(M+H)^+$ 306.0770, found 306.0769.

Data in agreement with literature values.[z]

***N*,*N*-Diethyl-2-(2-methoxyphenyl)ethynesulfonamide 165**

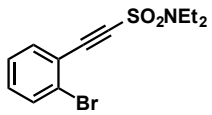


Synthesised using **156**, according to general procedure **E**.

Yellow oil, 37%; ν_{max} (film)/cm^{-1} 2978, 2940, 2878, 2179, 1597, 1491, 1355, 1260, 1150, 1016; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.46 (dd, *J* = 7.7, 1.7 Hz, 1H, $CH_3O(C)(C)CH$), 7.42 (dt, *J* = 7.8, 1.7 Hz, 1H, $CH_3O(C)CHCH$), 6.94 (dt, *J* = 7.5, 1.1 Hz, 1H, $CH_3O(C)CHCHCH$), 6.90 (d, *J* = 8.4 Hz, 1H, $CH_3O(C)CH$), 3.87 (s, 3H, CH_3O), 3.39 (q, *J* = 7.2 Hz, 4H, 2 x NCH_2CH_3), 1.30 (t, *J* = 7.2 Hz, 6H, 2 x NCH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 161.6 (C_q), 134.4 (CH), 132.7 (CH), 120.7 (CH), 110.9 (CH), 108.1 (C_q), 87.5 (C_q), 85.8 (C_q), 55.8 (CH_3), 42.9 (CH_2), 13.3 (CH_3); LRMS (CI) 268 (100); HRMS (CI) calc'd for $C_{13}H_{18}NO_3S$ $(M+H)^+$ 268.1002, found 268.0996.

Data in agreement with literature values.[z]

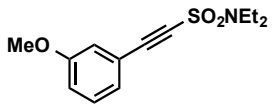
***N*,*N*-Diethyl-2-(2-bromophenyl)ethynesulfonamide 166**



Synthesised using **157**, according to general procedure **E**.

Pale yellow oil, 53%; ν_{max} (film)/cm^{-1} 2978, 2938, 2877, 2185, 1736, 1466, 1358, 1202, 1153, 1047, 1016; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.63 (dd, *J* = 7.3, 1.6 Hz, 1H, $Br(C)CH$), 7.57 (dd, *J* = 7.3, 1.6 Hz, 1H, $Br(C)(C)CH$), 7.33 (m, 2H, $Br(C)CHCH$ and $Br(C)CHCHCH$), 3.41 (q, *J* = 7.3 Hz, 4H, 2 x NCH_2), 1.31 (t, *J* = 7.3 Hz, 6H, 2 x NCH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 134.7 (CH), 132.9 (CH), 132.1 (CH), 127.5 (CH), 126.1 (C_q), 121.4 (C_q), 87.6 (C_q), 86.0 (C_q), 43.3 (CH_2), 13.8 (CH_3); LRMS (CI) 318 (100), 316 (98), 302 (50), 300 (47), 253 (44), 251 (45), 238 (7), 236 (6); HRMS (CI) calc'd for $C_{12}H_{15}BrNO_2S$ $(M+H)^+$ 316.0001, found 315.9992.

***N*,*N*-Diethyl-2-(3-methoxyphenyl)ethynesulfonamide 167**

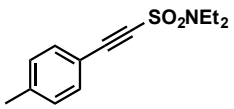


Synthesised using **158**, according to general procedure **E**.

Yellow oil, 34%; ν_{max} (film)/cm^{-1} 2977, 2940, 2876, 2176, 1576, 1357, 1156, 1016; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.29 (t, *J* = 7.8 Hz, 1H, $CH_3O(C)CHCH$), 7.12 (d, *J* = 7.6 Hz, 1H, $CH_3O(C)CHCHCH$), 7.03 (m, 1H, $CH_3O(C)CH(C)$), 7.01 (dd, *J* = 2.6, 8.3 Hz, 1H, $CH_3O(C)CHCH$), 3.81 (s, 3H, CH_3O), 3.38 (q, *J* = 7.2 Hz, 4H, 2 x NCH_2), 1.29 (t, *J* = 7.2 Hz, 6H, 2 x NCH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 159.5 (C_q), 130.0 (CH), 125.1 (CH), 119.6 (C_q), 117.7 (CH), 117.2 (CH), 88.2 (C_q), 83.6 (C_q), 55.5 (CH_3), 43.0 (CH_2), 13.5 (CH_3). LRMS (EI) 267 (32), 252 (100), 203 (70), 195 (98), 188 (15);

Data in agreement with literature values.[z]

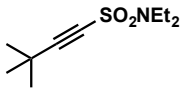
***N*,*N*-Diethyl-2-(4-methylphenyl)ethynesulfonamide 168**



Synthesised using **159**, according to general procedure **E**.

Pale yellow oil, 45%; ν_{max} (film)/cm^{-1} 2978, 2939, 2877, 2178, 1605, 1509, 1468, 1356, 1343, 1201, 1152, 1016; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.42 (d, *J* = 7.9 Hz, 2H, $CH_3(C)CHCH$), 7.19 (d, *J* = 7.9 Hz, 2H, $CH_3(C)CH$), 3.38 (q, *J* = 7.1 Hz, 4H, 2 x NCH_2CH_3), 2.39 (s, 3H, $CH_3(C)$), 1.29 (t, *J* = 7.1 Hz, 6H, 2 x NCH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 141.8 (C_q), 132.6 (CH), 129.6 (CH), 115.6 (C_q), 88.9 (C_q), 83.4 (C_q), 43.0 (CH_2), 21.8 (CH_3), 13.5 (CH_3); LRMS (CI) 252 (100), 236 (22), 187 (35), 179 (15); HRMS (CI) calc'd for $C_{13}H_{18}NO_2S$ $(M+H)^+$ 252.1053, found 252.1054.

***N*,*N*-Diethyl-2-*tert*butylethynesulfonamide 169**



Synthesised using **160**, according to general procedure **E**.

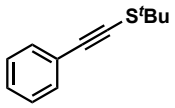
Pale yellow oil, 45%; ν_{max} (film)/cm^{-1} 2974, 2211, 2174, 1739, 1459, 1357, 1201, 1154, 1016; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 3.29 (q, J = 7.1 Hz, 4H, 2 x NCH_2CH$_3$), 1.28 (s, 9H, (C)(CH_3)$_3$), 1.24 (t, J = 7.2 Hz, 6H, 2 x NCH$_2$CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 98.5 (C_q), 75.0 (C_q), 42.7 (CH_2), 29.8 (CH_3), 27.8 (C_q), 13.2 (CH_3); LRMS (EI) 217 (7), 202 (100), 145 (6), 138 (3).

Data in agreement with literature values.[z]

General Procedure F: Synthesis of alkynyl sulfides 170–177

A 25 mL three-necked flask was flame-dried and flushed with argon, then charged with anhydrous THF (0.8 mL) and *tert*-butyl thiol (87.0 mg, 0.96 mmol, 4.0 eq). To the mixture was added KH (39.0 mg, 0.96 mmol, 4.0 eq, supplied as a 30% w/w suspension in mineral oil, which was washed with PE 40–60 °C, then dried between filter paper and used immediately) as a single portion. The resulting white paste was stirred at rt for 10 min, then gently heated to 50 °C for 20 min. The mixture was allowed to cool to rt, then further cooled to –40 °C. Dimethylamine solution (2.0 M in THF, 0.24 mL, 0.48 mmol, 2.0 eq) was added *via* syringe, immediately followed by alkynyl sulfonamide **161–169** (0.24 mmol, 1.0 eq). The resulting dark brown mixture was stirred at –40 °C for 10 min, then allowed to warm to rt. Excess potassium hydride was carefully quenched by addition of *i*-PrOH (1 mL), and the crude reaction mixture was diluted with CH_2Cl_2 (20 mL). The organic fraction was washed with water (10 mL) and saturated sodium chloride solution (10 mL). The organic portion was dried over $MgSO_4$, then filtered and concentrated *in vacuo*. Purification *via* column chromatography (0–5% EtOAc/PE) yielded alkynyl sulfides **170–177**.

***tert*-Butyl(phenylethynyl)sulfane 170**

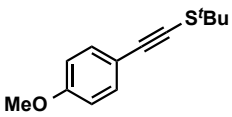


Synthesised using **161**, according to general procedure **F**.

Pale yellow oil, 64%; ν_{max} (film)/cm^{-1} 2963, 2922, 2897, 2164, 1596, 1487, 1456, 1365, 1162; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.44–7.42 (m, 2 H, *o*-Ar*H*), 7.32–7.28 (m, 3H, *m*- and *p*-ArH), 1.48 (s, 9H, (C*H*$_3$)$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 131.4 (CH), 128.4 (CH), 128.0 (CH), 123.9 (C_q), 96.2 (C_q), 79.1 (C_q), 48.6 (C_q), 30.5 (CH_3); LRMS (EI) 190 (19), 134 (100), 84 (23), 57 (33); HRMS (EI) calc'd for $C_{12}H_{14}S$ (M^+) 190.0816, found 190.0813.

Data in agreement with literature values.[aa]

***tert*-Butyl((4-methoxyphenyl)ethynyl)sulfane 171**

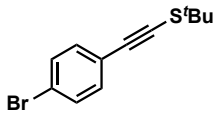


Synthesised using **162**, according to general procedure **F**.

Pale yellow oil, 32%; ν_{max} (film)/cm^{-1} 2963, 2163, 1603, 1507, 1288, 1247, 1162, 1026; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.39 (d, J = 8.6 Hz, 2H, $CH_3O(C)CHCH$), 6.83 (d, J = 8.6 Hz, 2H, $CH_3O(C)CHCH$), 3.81 (s, 3H, CH_3O), 1.46 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 159.6 (C_q), 133.4 (CH), 116.0 (C_q), 114.0 (CH), 95.9 (C_q), 77.0 (C_q), 55.4 (CH_3), 48.4 (C_q), 30.4 (CH_3); LRMS (EI) 220 (30), 164 (100), 149 (53), 97 (22), 86 (23), 84 (38); HRMS (EI) calc'd for $C_{13}H_{16}SO$ (M^+) 220.0916, found 220.0912.

[aa] Voets, M.; Smet, M.; Dehaen, W., *J. Chem. Soc., Perkin Trans. 1* **1999**, 1473

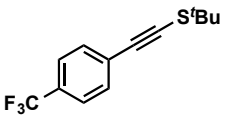
***tert*-Butyl((4-bromophenyl)ethynyl)sulfane 172**



Synthesised using **163**, according to general procedure **F**.

Pale yellow oil, 59%; ν_{max} (film)/cm^{-1} 2962, 2922, 2861, 2163, 1584, 1482, 1456, 1393, 1365, 1240, 1162, 1069; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.43 (d, *J* = 8.4 Hz, 2H, Br(C)C*H*CH), 7.27 (d, *J* = 8.4 Hz, 2H, Br(C)CHC*H*), 1.47 (s, 9H, S(C)(CH_3)$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 132.8 (CH), 131.6 (CH), 122.8 (C_q), 122.1 (C_q), 95.2 (C_q), 80.7 (C_q), 48.8 (C_q), 30.5 (CH_3); LRMS (EI) 270 (22), 268 (21), 214 (100), 212 (97), 169 (10), 167 (10), 132 (28); HRMS (EI) calc'd for $C_{12}H_{13}BrS$ (M^+) 267.9916, found 267.9915.

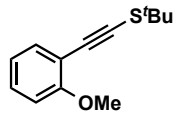
***tert*-Butyl((4-(trifluoromethyl)phenyl)ethynyl)sulfane 173**



Synthesised using **164**, according to general procedure **F**.

Colourless oil, 62%; ν_{max} (film)/cm^{-1} 2964, 2926, 2861, 2163, 1614, 1458, 1367, 1322, 1165, 1127, 1105, 1066, 1017; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.55 (d, *J* = 8.3 Hz, 2H, CF_3(C)C*H*CH), 7.49 (d, *J* = 8.3 Hz, 2H, CF_3(C)CHC*H*), 1.49 (s, 9H, S(C)(CH_3)$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 131.2 (CH), 129.3 (q, *J* = 32.7 Hz) (C_q), 127.6 (C_q), 125.3 (q, *J* = 3.6 Hz) (CH), 125.0 and 123.1 (q, *J* = 272.0 Hz) (C_q), 95.3 (C_q), 82.8 (C_q), 49.0 (C_q), 30.5 (CH_3); LRMS (EI) 258 (44), 202 (100), 183 (20), 173 (22), 157 (18), 130 (19); HRMS (EI) calc'd for $C_{13}H_{13}F_3S$ (M^+) 258.0685, found 258.0685.

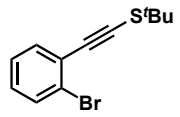
***tert*-Butyl((2-methoxyphenyl)ethynyl)sulfane 174**



Synthesised using **165**, according to general procedure **F**.

Colourless oil, 51%; ν_{max} (film)/cm^{-1} 2961, 2923, 2898, 2863, 2167, 1593, 1574, 1490, 1456, 1365, 1256, 1161, 1114, 1047; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.38 (dd, *J* = 7.7, 1.7 Hz, 1H, O(C)(C)C*H*), 7.25 (t, *J* = 7.8 Hz, 1H, O(C)CHC*H*), 6.89 (t, *J* = 7.4 Hz, 1H, O(C)CHCHC*H*), 6.86 (d, *J* = 8.4 Hz, 1H, O(C)C*H*), 3.87 (s, 3H, OCH_3), 1.49 (s, 9H, S(C)(CH_3)$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 160.0 (C_q), 132.9 (CH), 129.2 (CH), 120.5 (CH), 113.3 (C_q), 110.7 (CH), 92.5 (C_q), 83.1 (C_q), 55.9 (CH_3), 48.7 (C_q), 30.4 (CH_3); LRMS (EI) 220 (32), 164 (100), 148 (40), 135 (15), 131 (29), 121 (19); HRMS (EI) calc'd for $C_{13}H_{16}OS$ (M^+) 220.0916, found 220.0915.

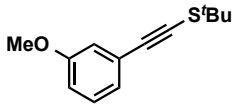
***tert*-Butyl((2-bromophenyl)ethynyl)sulfane 175**



Synthesised using **166**, according to general procedure **F**.

Pale yellow oil, 72%; ν_{max} (film)/cm^{-1} 2962, 2922, 2898, 2863, 2169, 1465, 1365, 1161, 1046, 1025; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.56 (d, *J* = 8.1 Hz, 1H, Br(C)C*H*), 7.42 (dd, *J* = 8.0, 1.3 Hz, 1H, Br(C)(C)C*H*), 7.24 (t, *J* = 7.6 Hz, 1H, Br(C)(C)CHC*H*), 7.12 (dt, *J* = 7.9, 1.5 Hz, 1H, Br(C)CHC*H*), 1.53 (s, 9H, S(C)(CH_3)$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 132.7 (CH), 132.4 (CH), 128.8 (CH), 127.1 (CH), 126.0 (C_q), 124.8 (C_q), 94.9 (C_q), 84.8 (C_q), 49.4 (C_q), 30.6 (CH_3); LRMS (EI) 270 (10), 268 (9), 214 (53), 212 (52), 132 (31), 86 (30), 84 (48); HRMS (EI) calc'd for $C_{12}H_{13}BrS$ (M^+) 267.9916, found 267.9916.

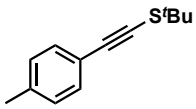
***tert*-Butyl((3-methoxyphenyl)ethynyl)sulfane 176**



Synthesised using **167**, according to general procedure **F**.

Pale yellow oil, 49%; ν_{max} (film)/cm^{-1} 2962, 2158, 1601, 1573, 1456, 1365, 1283,1042; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.21 (t, J = 7.9 Hz, 1H, O(C)CHC*H*), 7.03 (d, J = 7.6 Hz, 1H, O(C)CHCHC*H*), 6.95 (s, 1H, O(C)C*H*(C)), 6.85 (ddd, J = 8.3, 2.6, 0.9 Hz, 1H, O(C)C*H*CH), 3.80 (s, 3H, OC*H*$_3$), 1.48 (s, 9H, C(C*H*$_3$)$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 159.4 (C_q), 129.5 (CH), 124.8 (C_q), 124.0 (CH), 116.2 (CH), 114.6 (CH), 96.2 (C_q), 79.0 (C_q), 55.4 (CH_3), 48.6 (C_q), 30.5 (CH_3); LRMS (CI) 220 (50), 164 (100), 135 (6), 86 (4), 84 (4); HRMS (CI) calc'd for $C_{13}H_{16}OS$ (M^+) 220.0922, found 220.0921.

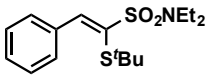
***tert*-Butyl((4-methylphenyl)ethynyl)sulfane 177**



Synthesised using **168**, according to general procedure **F**.

Yellow oil, 62%; ν_{max} (film)/cm^{-1} 2963, 2922, 2897, 2864, 2164, 1508, 1455, 1365, 1162, 1020; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.33 (d, J = 8.1 Hz, 2H, CH_3(C)CHC*H*), 7.11 (d, J = 8.1 Hz, 2H, CH_3(C)C*H*), 2.34 (s, 3H, C*H*$_3$(C)CH), 1.47 (s, 9H, (C)(C*H*$_3$)$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 138.2 (C_q), 131.5 (CH), 129.1 (CH), 120.8 (C_q), 96.3 (C_q), 78.0 (C_q), 48.4 (C_q), 30.4 (CH_3), 21.6 (CH_3); LRMS (EI) 204 (16), 148 (100), 86 (49), 84 (77); HRMS (EI) calc'd for $C_{13}H_{16}S$ (M^+) 204.0967, found 204.0969.

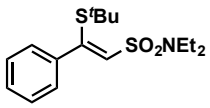
(*E*)-1-(*tert*-Butylthio)-*N*,*N*-diethyl-2-phenylethene-1-sulfonamide 151



Synthesised using **161**, according to general procedure **F**.

Colourless oil, 55%; ν_{max} (film)/cm^{-1} 2965, 2923, 1586, 1455, 1341, 1137, 1014; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 8.19 (s, 1H, PhC*H*), 8.02 (dd, *J* = 7.8, 2.8 Hz, 2H, *o*-Ar*H*), 7.42–7.37 (m, 3H, *m*- and *p*-Ar*H*), 3.36 (q, *J* = 7.0 Hz, 4H, 2 x NCH_2CH$_3$), 1.32 (s, 9H, S(C)(CH_3)$_3$), 1.19 (t, *J* = 7.0 Hz, 6H, 2 x NCH$_2$CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 147.6 (CH), 134.3 (C_q), 134.1 (C_q), 131.1 (CH), 130.5 (CH), 128.5 (CH), 52.2 (C_q), 43.0 (CH_2), 32.0 (CH_3), 14.8 (CH_3); LRMS (CI) 328 (5), 281 (12), 272 (24), 191 (52), 134 (54), 74 (100); HRMS (CI) calc'd for $C_{16}H_{26}NO_2S_2$ ($M+H^+$) 328.1405, found 328.1398.

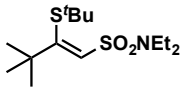
(*Z*)-2-(*tert*-Butylthio)-*N*,*N*-diethyl-2-phenylethene-1-sulfonamide 150



Synthesised using **161**, according to general procedure **F**.

Colourless oil, 17%; ν_{max} (film)/cm^{-1} 2970, 1737, 1328, 1201, 1131, 1018; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.53 (dd, *J* = 8.3, 1.4 Hz, 2H, *o*-Ar*H*), 7.42–7.35 (m, 3H, *m*- and *p*-Ar*H*), 6.62 (s, 1H, C*H*SO$_2$), 3.38 (q, *J* = 7.1 Hz, 4H, 2 x NCH_2CH$_3$), 1.22 (t, *J* = 7.1 Hz, 6H, 2 x NCH$_2$CH_3), 1.16 (s, 9H, S(C)(CH_3)$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 150.9 (C_q), 140.4 (C_q), 134.9 (CH), 129.9 (CH), 128.7 (CH), 128.5 (CH), 49.4 (C_q), 42.1 (CH_2), 32.0 (CH_3), 14.6 (CH_3); LRMS (EI) 327 (3), 271 (15), 207 (9), 134 (100); HRMS (EI) calc'd for $C_{16}H_{25}NO_2S_2$ (M^+) 327.1327, found 327.1329.

(*Z*)-2-(*tert*-Butylthio)-*N*,*N*-diethyl-3,3-dimethylbut-1-ene-1-sulfonamide 179



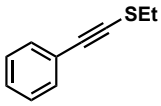
Synthesised using **169**, according to general procedure **F**.

Colourless oil, 54%; ν_{max} (film)/cm^{-1} 2967, 2873, 1565, 1460, 1336, 1200, 1146, 1016; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 6.71 (s, 1H, C*H*SO$_2$), 3.29 (q, *J* = 7.3 Hz, 4H, 2 x NC*H*$_2$CH$_3$), 1.46 (s, 9H, (C*H*$_3$)$_3$(C)S), 1.19 (s, 9H, (C*H*$_3$)$_3$(C)(C)), 1.17 (t, *J* = 7.3 Hz, 6H, 2 x NCH$_2$C*H*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 157.8 (C_q), 134.6 (CH), 50.8 (C_q), 41.6 (CH_2), 41.0 (C_q), 32.7 (CH_3), 29.8 (CH_3), 14.3 (CH_3); LRMS (EI) 307 (1), 251 (16), 194 (14), 114 (100); HRMS (CI) calc'd for $C_{14}H_{29}NO_2S_2$ (M^+) 307.1634, found 307.1638.

General Procedure G: Synthesis of alkynyl sulfides 181–185

To a flame-dried flask flushed with argon were added thiol (0.76 mmol, 4.0 eq) and anhydrous THF (0.7 mL). To the solution was added KH (30 mg, 0.76 mmol, 4.0 eq) as a single portion, and the white paste was stirred at rt for 10 min, before being gently heated to 40 °C for 20 min. The solution was allowed to cool to rt, then cooled further to –40 °C. To the cooled solution was added *N*,*N*-dimethylamine solution (2.0 M in THF, 0.38 mmol, 2.0 eq), followed immediately after by sulfonamide **161**. The mixture was stirred at –40 °C for 10 min, before being allowed to warm to rt. Excess KH was quenched by addition of *i*-PrOH (1 mL), and the crude product was diluted with CH_2Cl_2 (20 mL). The organic portion was washed with H_2O (10 mL) and saturated sodium chloride solution (10 mL), then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified *via* column chromatography (0–5% EtOAc/PE) to yield alkynyl sulfides **181–185**.

Ethyl(phenylethynyl)sulfane 181

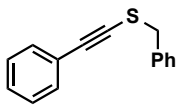


Synthesised using ethanethiol, according to general procedure **G**.

Colourless oil, 59%; ν_{max} (film)/cm^{-1} 2965, 2926, 2869, 2165, 1595, 1486, 1442, 1375, 1263, 1069; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.42–7.40 (m, 2H, *o*-Ar*H*), 7.31–7.28 (m, 3H, *m*- and *p*-Ar*H*), 2.82 (q, *J* =7.3 Hz, 2H, SC*H*$_2$CH$_3$), 1.46 (t, *J* = 7.3 Hz, 3H, SCH$_2$C*H*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 131.5 (CH), 128.4 (CH), 128.1 (CH), 123.6 (C_q), 93.6 (C_q), 79.3 (C_q), 30.1 (CH_2), 14.9 (CH_3); LRMS (CI) 224 (23), 163 (100), 134 (45), 129 (49); HRMS (CI) calc'd for $C_{10}H_{11}S$ ($M+H^+$) 163.0576, found 163.0573.

Data in agreement with literature values.[bb]

Benzyl(phenylethynyl)sulfane 182



Synthesised using benzylthiol, according to general procedure **G**.

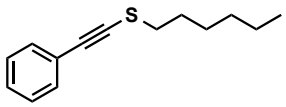
Colourless oil, 24%; ν_{max} (film)/cm^{-1} 3061, 3029, 2925, 2853, 2166, 1596, 1487, 1453, 1419, 1237, 1201, 1070; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.40–7.27 (m, 10H, Ar*H*), 4.02 (s, 2H, SC*H*$_2$Ph); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 136.7 (C_q), 131.4 (CH), 129.3 (CH), 128.7 (CH), 128.4 (CH), 128.2 (CH), 127.9 (CH), 123.5 (C_q), 94.7 (C_q), 79.2 (C_q), 40.6 (CH_2). LRMS (CI) 224 (58), 213 (30), 191 (100), 181 (10), 147 (17); HRMS (CI) calc'd for $C_{15}H_{12}S$ (M^+) 224.0654, found 224.0651.

Data in agreement with literature values.[cc]

[bb] Voets, M.; Smet, M.; Dehaen, W., *J. Chem. Soc. Perkin Trans. 1*, **1999**, 1473

[cc] Hossain, M. S.; Schwan, A. L., *Org. Lett.* **2011**, *13*, 5330

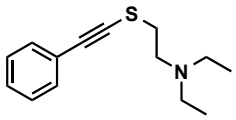
Hexyl(phenylethynyl)sulfane 183



Synthesised using 1-hexanethiol, according to general procedure **G**.

Pale yellow oil, 62%; ν_{max} (film)/cm^{-1} 2956, 2927, 2856, 2166, 1595, 1486, 1464, 1441, 1378, 1259, 1069; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.41–7.39 (m, 2H, *o*-Ar*H*), 7.30–7.27 (m, 3H, *m*- and *p*-ArH), 2.80 (t, *J* = 7.4 Hz, 2H, SCH_2), 1.80 (quint, *J* = 7.4 Hz, 2H, SCH_2CH_2), 1.48–1.43 (m, 2H), 1.34–1.32 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H, $S(CH_2)_5CH_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 131.5 (CH), 128.4 (CH), 128.0 (CH), 123.7 (C_q), 92.9 (C_q), 79.8 (C_q), 35.9 (CH_2), 31.4 (CH_2), 29.4 (CH_2), 28.1 (CH_2), 22.7 (CH_2), 14.2 (CH_3); LRMS (CI) 218 (100), 134 (10), 129 (4); HRMS (CI) calc'd for $C_{14}H_{18}S$ (M^+) 218.1124, found 218.1123.

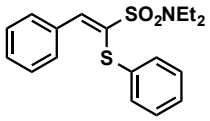
***N*,*N*-Diethyl-2-((phenylethynyl)thio)ethan-1-amine 184**



Synthesised using 2-(*N*,*N*-diethylamino)ethane-1-thiol, according to general procedure **G**.

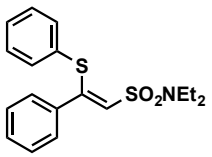
Pale yellow oil, 56%; ν_{max} (film)/cm^{-1} 2968, 2932, 2803, 2164, 1595, 1487, 1442, 1383, 1285, 1200, 1068; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.40–7.38 (m, 2H, *o*-Ar*H*), 7.30–7.27 (m, 3H, *m*- and *p*-Ar*H*), 2.89 (apparent s, 4H, SCH_2CH_2N), 2.59 (q, *J* = 7.2 Hz, 4H, 2 x NCH_2CH_3), 1.06 (t, *J* = 7.2Hz, 6H, 2 x NCH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 131.5 (CH), 128.4 (CH), 128.1 (CH), 123.6 (C_q), 92.9 (C_q), 79.6 (C_q), 52.1 (CH_2), 47.3 (CH_2), 33.5 (CH_2), 12.1 (CH_3); LRMS (CI) 234 (100), 218 (13), 205 (81), 161 (7); HRMS (CI) calc'd for $C_{14}H_{20}NS$ ($M+H^+$) 234.1311, found 234.1310.

(*E*)-*N*,*N*-Diethyl-2-phenyl-1-(phenylthio)ethene-1-sulfonamide 185a



Synthesised using thiophenol, according to general procedure **G**.
Colourless oil, 3%; ν_{max} (film)/cm^{-1} 2977, 2933, 2256, 1583, 1441, 1323, 1202, 1140, 1019; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 8.27 (s, 1H, PhC*H*), 7.87 (d, *J* = 7.12 Hz, 2H, *o*-Ar*H*), 7.39–7.33 (m, 4H, Ar*H*), 7.29–7.22 (m, 4H, Ar*H*), 7.15 (t, *J* = 7.2 Hz, 1H, *p*-Ar*H*), 3.30 (q, *J* = 7.3 Hz, 4H, 2 x NC*H*$_2$CH$_3$), 1.18 (t, *J* = 7.3 Hz, 6H, 2 x NCH$_2$C*H*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 147.2 (CH), 133.9 (C_q), 132.7 (C_q), 131.8 (C_q), 131.1 (CH), 131.0 (CH), 129.3 (CH), 128.8 (CH), 128.0 (CH), 127.4 (CH), 126.6 (CH), 43.3 (CH_2), 15.1 (CH_3); LRMS (CI) 347 (40), 211 (100), 178 (26), 109 (3); HRMS (CI) calc'd for $C_{18}H_{21}NO_2S_2$ (M^+) 347.1008, found 347.1009.

(*Z*)-*N*,*N*-Diethyl-2-phenyl-2-(phenylthio)ethene-1-sulfonamide 185b

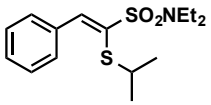


Synthesised using thiophenol, according to general procedure **G**.
Colourless oil, 67%; ν_{max} (film)/cm^{-1} 2979, 2254, 1547, 1468, 1329, 1200, 1140, 1016; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.21 (dd, *J* = 6.5, 1.4 Hz, 2H, *o*-Ar*H*), 7.16–7.12 (m, 5H, Ar*H*), 7.08–7.03 (m, 3H, Ar*H*), 6.42 (s, 1H, C*H*SO$_2$), 3.45 (q, *J* = 7.0 Hz, 4H, 2 x NC*H*$_2$CH$_3$), 1.28 (t, *J* = 7.0 Hz, 6H, 2 x NCH$_2$C*H*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 152.7 (C_q), 137.1 (C_q), 133.5 (CH), 131.8 (C_q), 129.2 (CH), 128.8 (CH), 128.7 (CH), 128.2 (CH), 128.0 (CH), 126.3 (CH), 41.9 (CH_2), 14.5 (CH_3); LRMS (EI) 347 (18), 275 (25), 211 (100), 178 (23), 165 (8), 121 (13), 109 (15); HRMS (EI) calc'd for $C_{18}H_{21}NO_2S_2$ (M^+) 347.1008, found 347.1005.

General Procedure H: Synthesis of *alpha*-addition products 188–189

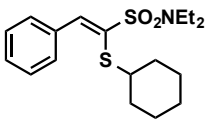
Reactions were conducted as for General Procedure **G**, though with sulfonamide **161** predissolved in H_2O:THF (5:95, 1 mL). *Alpha*-addition products **188–189** were isolated upon purification *via* column chromatography (0–5% EtOAc/PE).

(*E*)-*N*,*N*-Diethyl-1-(*iso*-propylthio)-2-phenylethene-1-sulfonamide 188



Synthesised using propane-2-thiol, according to general procedure **H**.
Colourless oil, 89%; ν_{max} (film)/cm^{-1} 2970, 2930, 2867, 1446, 1320, 1201, 1138, 1016; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 8.03 (s, 1H, S(C)C*H*), 7.95 (m, 2H, *o*-Ar*H*), 7.42–7.38 (m, 3H, *m*- and *p*-Ar*H*), 3.67 (sept, *J* = 6.6 Hz, 1H, SC*H*), 3.38 (q, *J* = 7.1 Hz, 4H, 2 x NC*H*$_2$CH$_3$), 1.23–1.20 (m, 12H, 2 x NCH$_2$C*H*$_3$ and 2 x SCHC*H*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 144.8 (CH), 134.5 (C_q), 133.5 (C_q), 131.0 (CH), 130.3 (CH), 128.5 (CH), 43.1 (CH_2), 40.4 (CH), 23.0 (CH_3), 14.9 (CH_3); LRMS (CI) 313 (39), 177 (100), 135 (12); HRMS (CI) calc'd for $C_{15}H_{23}NO_2S_2$ (M^+) 313.1165, found 313.1166.

(*E*)-1-(Cyclohexylthio)-*N*,*N*-diethyl-2-phenylethene-1-sulfonamide 189



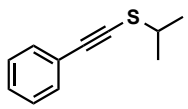
Synthesised using cyclohexanethiol, according to general procedure **H**.
Pale yellow oil, 90%; ν_{max} (film)/cm^{-1} 2929, 2853, 1446, 1321, 1201, 1139, 1017, 943; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 8.03 (s, 1H, S(C)C*H*), 7.96–7.94 (m, 2H, *o*-Ar*H*), 7.41–7.38 (m, 3H, *m*- and *p*-Ar*H*), 3.45–3.40 (m, 1H, SC*H*), 3.37 (q, *J* = 7.2 Hz, 4H, 2 x NC*H*$_2$CH$_3$), 1.92–1.90 (m, 2H, cy*H*), 1.67–1.63 (m, 2H, cy*H*), 1.54–1.52 (m, 1H, cy*H*), 1.31–1.14 (m, 11 H, 5 x cy*H* and 2 x NCH$_2$C*H*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 145.0 (CH), 133.8 (C_q), 133.6 (C_q), 131.0 (CH), 130.3 (CH), 128.5 (CH), 48.5 (CH),

43.2 (CH_2), 33.3 (CH_2), 26.0 (CH_2), 25.7 (CH_2), 14.9 (CH_3); LRMS (CI) 353 (32), 217 (100), 134 (17); HRMS (CI) calc'd for $C_{18}H_{27}NO_2S_2$ (M^+) 353.1478, found 353.1479.

General Procedure I: Synthesis of alkynyl sulfides 186–187

To a flame-dried flask flushed with argon were added *alpha*-addition products **188–189** (0.07–0.16 mmol, 1.0 eq) and anhydrous THF (2.0 mL). The solution was cooled to –78 °C, and lithium di*iso*propylamide solution (1.8 M in THF/heptanes/ethylbenzene, 2.0 eq) was added dropwise. The yellow solution was stirred at –78 °C for 30 min, then allowed to reach rt. The crude reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with water (10 mL) and saturated sodium chloride solution (10 mL). The organic portion was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification *via* column chromatography (0–5% EtOAc/PE) yielded alkynyl sulfides **186–187**.

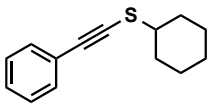
iso-Propyl(phenylethynyl)sulfane 186



Synthesised using **188**, according to general procedure **I**.
Pale yellow oil, 77%; ν_{max} (film)/cm^{-1} 2958, 2924, 2854, 2165, 1596, 1487, 1455, 1380, 1238, 1155, 1069; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.43–7.41 (m, 2H, *o*-Ar*H*), 7.30–7.28 (m, 3H, *m*- and *p*-Ar*H*), 3.26 (sept, *J* = 6.8 Hz, 1H, SC*H*(CH_3)$_2$), 1.44 (d, *J* = 6.8 Hz, 6H, 2 x SCHC*H*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 131.5 (CH), 128.4 (CH), 128.0 (CH), 123.7 (C_q), 94.9 (C_q), 78.7 (C_q), 40.0 (CH), 23.1 (CH_3); LRMS (EI) 176 (37), 134 (100); HRMS (EI) calc'd for $C_{11}H_{12}S$ (M^+) 176.0654, found 176.0654.
Data in agreement with literature values.[dd]

[dd] Zheng, W.; Zheng, F.; Hong, Y.; Hu, L., *Heteroatom Chem.* **2012**, *23*, 105

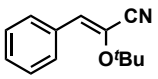
Cyclohexyl(phenylethynyl)sulfane 187



Synthesised using **189**, according to general procedure **I**.

Colourless oil, 71%; ν_{max} (film)/cm^{-1} 2928, 2853, 2164, 1486, 1447, 1262, 1201; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.42–7.41 (m, 2H, *o*-Ar*H*), 7.31–7.27 (m, 3H, *m* and *p*-Ar*H*), 3.00 (tt, *J* = 7.2, 3.5 Hz, 1H, SC*H*), 2.11 (m, 2H, 2 x SCHC*H*), 1.83 (dt, *J* = 13.5, 3.7 Hz, 2H, 2 x SCHCH$_2$C*H*), 1.67–1.63 (m, 1H, SCHCH$_2$CH$_2$C*H*), 1.56 (dq, *J* = 11.9, 3.4 Hz, 2H, 2 x SCHC*H*), 1.37 (tq, *J* = 11.9, 3.4 Hz, 2H, 2 x SCHCH$_2$C*H*), 1.30–1.24 (m, 1H, SCHCH$_2$CH$_2$C*H*); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 131.5 (CH), 128.4 (CH), 128.0 (CH), 123.8 (C_q), 94.5 (C_q), 78.7 (C_q), 47.8 (CH), 33.1 (CH_2), 26.2 (CH_2), 25.6 (CH_2); LRMS (EI) 216 (26), 134 (100); HRMS (EI) calc'd for $C_{14}H_{16}S$ (M^+) 216.0967, found 216.0968.

(*Z*)-2-(*tert*-Butoxy)-3-phenylacrylonitrile 192



To a 25 mL flame-dried flask was added KO^{t}Bu (176 mg, 1.57 mmol, 4.0 eq) and $HNMe_2$ (2.0 M in THF, 0.40 mL, 0.79 mmol, 2.0 eq) under an argon atmosphere. The pale yellow solution was diluted with anhydrous THF (0.5 mL) and stirred at rt for 5 min. To the mixture was added 3-phenyl-2-propynenitrile (0.39 mmol, 1.0 eq.), and the dark red solution was stirred at rt for 10 min. The crude reaction mixture was diluted in CH_2Cl_2 (20 mL) and washed with water (10 mL) and brine (10 mL). The organic portions were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude brown oil was purified *via* flash chromatography (0–5% EtOAc/PE) to yield **192**.

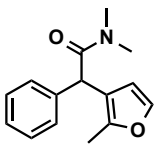
Pale yellow oil, 4%; ν_{max} (film)/cm^{-1} 2982, 2928, 2210, 1730, 1623, 1447, 1369, 1120, 1077; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.69 (d, *J* = 7.2 Hz, 2H, *o*-Ar*H*), 7.35 (t, *J* = 7.2 Hz, 2H, *m*-Ar*H*), 7.31 (t, *J* = 7.2 Hz, 1H, *p*-Ar*H*), 6.39 (s, 1H, O^{t}Bu(C)C*H*), 1.51 (s,

9H, O(C)(CH_3)$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 133.4 (C_q), 130.0 (CH), 129.3 (CH), 129.2 (CH), 128.6 (CH), 124.5 (C_q), 118.3 (C_q), 83.2 (C_q), 28.6 (CH_3); LRMS (CI) 202 (58), 174 (16), 146 (49), 118 (39), 91 (39), 85 (53), 51 (100); HRMS (CI) calc'd for $C_{13}H_{16}NO$ $(M+H)^+$ 202.1226, found 202.1218.

General procedure J: Synthesis of ynol ethers

In a flame-dried flask under an atmosphere of argon was added anhydrous THF (1.0 mL) and an alcohol (0.54 mmol, 2.0 eq). To this was added potassium hydride (supplied as a 30% suspension in mineral oil, washed with PE and dried between filter paper immediately prior to use, 43.0 mg, 1.08 mmol, 4.0 eq) as a single portion. The mixture was stirred at rt for 10 min, then gently heated to 50 °C for 20 min. The white paste was then allowed to cool to rt, then further cooled to 0 °C. To the cooled solution was added *N*,*N*-dimethylamine (2.0 M solution in THF, 270 μL, 2.0 eq), immediately followed by **161**. The dark brown solution was stirred at 0 °C for 10 min, then allowed to warm to rt and quenched by addition of *i*PrOH (1 mL). The crude product was dissolved in CH_2Cl_2 (20 mL), and washed with water (10 mL) and brine (10 mL). The organic portion was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification *via* column chromatography (0–5% EtOAc/PE) yielded **198**.

_N_,_N_-Dimethyl-2-(2-methylfuran-3-yl)-2-phenylacetamide 198

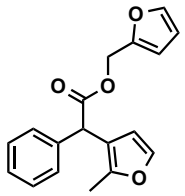


Synthesised using furfuryl alcohol, according to general procedure **J**.

Pale yellow oil, 47%; ν_{max} (film)/cm^{-1} 2920, 1642, 1512, 1494, 1452, 1391, 1257, 1219, 1129, 1093; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.32–7.30 (t, J = 7.7 Hz, 2H, *o*-Ar*H*), 7.26–7.22 (m, 4H, *m*- and *p*-Ar*H* and OC*H*), 6.39 (s, 1H, OCHC*H*), 5.01 (s, 1H, PhC*H*), 3.02 (s, 3H, NCH_3), 3.00 (s, 3H, NCH_3), 2.23 (s, 3H, O(C)CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 171.8 (C_q), 147.8 (C_q), 140.3 (CH), 139.6 (C_q), 128.7 (CH), 128.4 (CH), 127.0 (CH), 118.0 (C_q), 112.1 (CH), 45.5 (CH), 37.6 (CH_3), 36.2 (CH_3),

11.9 (CH_3); LRMS (ESI) 245 (13), 244 (100), 232 (5); HRMS (ESI) calc'd for $C_{15}H_{18}NO_2$ ($M+H^+$) 244.1338, found 244.1342.

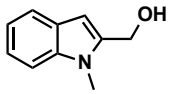
Furan-2-ylmethyl 2-(2-methylfuran-3-yl)-2-phenylacetate 199



In a flame-dried, sealed tube under an atmosphere of argon, furfuryl alcohol (83 mg, 0.84 mmol, 4.0 eq) was dissolved in anhydrous THF (1.5 mL). To the solution was added potassium hydride (35 mg, 0.84 mmol, 4.0 eq) as a single portion. The potassium salt was formed as in General Procedure **J**. The organic solvent was removed *in vacuo*, and the crude salt redissolved in toluene (2 mL). To the crude mixture was added **161** (50 mg, 0.21 mmol, 1.0 eq) as a single burst at rt to give a dark brown solution. After stirring at rt for 2 h, the mixture was quenched by addition of *i*PrOH (1 mL). The crude mixture was dissolved in CH_2Cl_2 (20 mL) and washed with water (10 mL) and brine (10 mL), then dried over $MgSO_4$. The crude solution was filtered, concentrated *in vacuo* and purified *via* column chromatography to yield **199**.

Colourless oil, 36%; ν_{max} (film)/cm^{-1} 2924, 1736, 1497, 1453, 1368, 1224, 1152, 1093; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.42 (s, 1H, OC*H*CHCH), 7.32–7.25 (m, 6H, 5 x Ar*H* and OC*H*CH(C)), 6.43 (s, 1H, OCHC*H*(C)), 6.37 (m, 1H, O(C)C*H*CH), 6.36 (m, 1H, O(C)CHC*H*CH), 5.13 (s, 2H, OCH_2), 4.85 (s, 1H, PhC*H*), 2.19 (s, 3H, (C)CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 172.1 (C_q), 149.3 (C_q), 148.8 (C_q), 143.4 (CH), 140.3 (CH), 138.4 (C_q), 128.7 (CH), 128.1 (CH), 127.4 (CH), 116.6 (C_q), 111.4 (CH), 111.0 (CH), 110.7 (CH), 58.8 (CH_2), 47.9 (CH), 11.8 (CH_3); LRMS (ESI) 297 (100), 244 (80), 224 (17); HRMS (ESI) calc'd for $C_{18}H_{17}O_4$ ($M+H^+$) 297.1127, found 297.1126.

(1-Methyl-1*H*-indol-2-yl)methanol 200

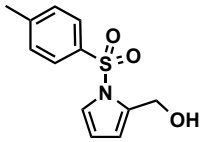


In a flame dried flask flushed with argon, ethyl indole-2-carboxylate (600 mg, 3.17 mmol, 1.0 eq) was dissolved in anhydrous DMF (10 mL). The mixture was cooled to 0 °C, and NaH (~60% dispersion in mineral oil, 150 mg, 3.81 mmol, 1.2 eq) was added in small portions. The solution was removed from the cooling bath, and stirred at rt for 15 min, before MeI (750 μL, 12.70 mmol, 4.0 eq) was added as a single burst. The solution was stirred at rt for a further 40 min. The mixture was quenched by addition of 10% NH_4Cl solution (100 mL), and washed with Et_2O (3 x 50 mL). The organic portions were combined and washed with water (50 mL), and solvent removed *in vacuo*. In a flame-dried flask flushed with argon, the crude product was dissolved in anhydrous THF, and cooled to –78 °C. $LiAlH_4$ (1.0 M in THF, 6.97 mL, 6.97 mmol, 2.2 eq) was added dropwise, and the solution stirred at –78 °C for 1 h. The reaction mixture was allowed to warm to rt over 30 min, then quenched by addition of Et_2O (20 mL) then 20% KOH solution (1 mL) *via* syringe. The white precipitate formed was collected *via* suction filtration to give the pure product **200**.

White solid, 72%; mp = 99–100 °C (lit. = 100–101 °C)[ee]; ν_{max} (film)/cm^{-1} 3311, 2928, 1468, 1397, 1338, 1313, 1215, 1137; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.60 (d, J = 7.8 Hz, 1H, N(C)(C)C*H*), 7.33 (d, J = 8.0 Hz, 1H, N(C)C*H*), 7.25 (t, J = 7.6 Hz, 1H, N(C)CHC*H*), 7.12 (t, J = 7.5 Hz, 1H, N(C)CHCHC*H*), 6.46 (s, 1H, N(C)C*H*), 4.81 (brs, 2H, CH_2OH), 3.81 (s, 3H, NCH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 138.7 (C_q), 138.2 (C_q), 127.2 (C_q), 122.1 (CH), 120.9 (CH), 119.7 (CH), 109.3 (CH), 101.5 (CH), 57.6 (CH_2), 30.0 (CH_3).
Data in agreement with literature values.[ee]

[ee] Chen, W.; Sana, K.; Jiang, Y.; Meyer, E. V. S.; Lapp, S.; Galinski, M. R.; Liebeskind, L. S., *Organometallics*, **2013**, *32*, 7594

(1-Tosyl-1*H*-pyrrol-2-yl)methanol 201



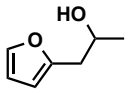
In a flame-dried flask under an argon atmosphere, pyrrole-2-carboxaldehyde was dissolved in anhydrous THF (10 mL) and cooled to 0 °C. NaH (~60% dispersion in mineral oil, 200 mg, 5.04 mmol, 1.2 eq) was added as small portions, and the mixture stirred for 15 min at rt. *p*-Toluenesulfonyl chloride (1.12 g, 5.89 mmol, 1.4 eq) dissolved in anhydrous THF (5 mL) was added dropwise, and the mixture stirred at rt for 1 h. The reaction was quenched by careful addition of water (10 mL), and the organic solvent was removed *in vacuo*. The aqueous solution was extracted with CH_2Cl_2 (3 x 50 mL), and the organic layer was then washed with saturated sodium bicarbonate solution (20 mL), water (20 mL) and brine (20 mL). After removal of organic solvent *in vacuo*, the crude material was dissolved in anhydrous MeOH (15 mL) and cooled to 0 °C. $NaBH_4$ (145 mg, 3.86 mmol, 1.2 eq) was added as small portions, and the reaction stirred at rt for 3 h. The reaction was quenched by careful addition of water (10 mL), and extracted with Et_2O (3 x 20 mL). The organic portions were combined, washed with water (20 mL) and brine (20 mL), then dried over $MgSO_4$. Filtration, removal of solvent *in vacuo* and purification *via* column chromatography (0–20% EtOAc/PE) yielded the product **201**.

Pale pink solid, 77%; mp = 97–98 °C (lit = 97 °C)[ff]; ν_{max} (film)/cm^{-1} 3342, 1596, 1357, 1234, 1190, 1170, 1145, 1087, 1053; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.71 (d, J = 8.5 Hz, 2H, S(C)C*H*), 7.31 (d, J = 8.5 Hz, 2H, CH_3(C)C*H*), 7.27–7.26 (m, 1H, NC*H*), 6.26 (dd, J = 3.4, 1.7 Hz, 1H, NCHC*H*), 6.24 (t, J = 3.4 Hz, 1H, N(C)C*H*), 4.60 (s, 2H, HOC*H*$_2$), 2.42 (s, 3H, C*H*$_3$Ar); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 145.4 (C_q), 136.1 (C_q), 134.6 (C_q), 130.3 (CH), 126.8 (CH), 123.7 (CH), 115.4 (CH), 112.0 (CH), 57.0 (CH_2), 21.8 (CH_3); LRMS (CI) 269 (28), 251 (100), 234 (22).

[ff] Prinzbach, H.; Bringmann, H.; Fritz, H.; Markert, J.; Knothe, L.; Eberbach, W.; Brokatzky-Geiger, J.; Sekutowski, J. C.; Krüger, C., *Chem. Ber.*, **1986**, *119*, 616

Data in agreement with literature values[gg]

1-(Furan-2-yl)propan-2-ol 202



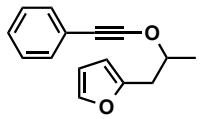
To a flame dried flask under an atmosphere of argon was added furan (1.36 g, 20 mmol, 1.0 eq) and anhydrous THF (50 mL). The solution was cooled to –40 °C, and ^{n}BuLi (2.5 M in hexanes, 9.6 mL, 24 mmol, 1.2 eq) was added dropwise. The solution was stirred at –40 °C for 30 min, and then at rt for a further 2 h. The reaction mixture was cooled to 0 °C, and propylene oxide (1.16 g, 20 mmol, 1.0 eq) added dropwise. The reaction was stirred at rt for a further 3 h, then quenched *via* addition of saturated NH_4Cl solution (100 mL). The organic portion was extracted with CH_2Cl_2 (3 x 100 mL), then dried over Na_2SO_4. The crude product was filtered, concentrated *in vacuo*, and purified *via* column chromatography (0–20% EtOAc/PE) to yield alcohol **202**.

Pale yellow oil, 30%; ν_{max} (film)/cm^{-1} 3364, 2970, 2930, 1712, 1597, 1507, 1456, 1375, 1145, 1114; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.35 (d, *J* = 1.2 Hz, 1H, OC*H*CH), 6.32 (dd, *J* = 3.0, 2.1 Hz, 1H, OCHC*H*), 6.11 (d, *J* = 3.0 Hz, 1H, OCHCHC*H*), 4.13–4.07 (m, 1H, HOC*H*), 2.82 (dd, *J* = 14.9, 4.4 Hz, 1H, O(C)CH_2), 2.74 (dd, *J* = 14.9, 7.8 Hz, 1H, O(C)CH_2), 1.24 (d, *J* = 6.2 Hz, 3H, CH_3CH); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 152.9 (C_q), 141.8 (CH), 110.4 (CH), 107.1 (CH), 66.9 (CH), 37.9 (CH_2), 22.8 (CH_3); LRMS (EI) 126 (30), 109 (11), 95 (14), 82 (100), 81 (85); HRMS (EI) calc'd for $C_7H_{10}O_2$ (M^+) 126.0675, found 126.0678.
Data in agreement with literature values.[hh]

[gg] Abell, A. D.; Nabbs, B. K.; Battersby, A. R., *J. Org. Chem.*, **1998**, *63*, 8163

[hh] Wu, H. -J.; Lin, S. -H.; Lin, C. -C., *Heterocycles*, **1994**, *38*, 1507

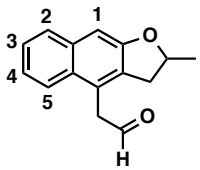
2-(2-((Phenylethynyl)oxy)propyl)furan 203



Synthesised using **202**, according to general procedure **J**.

Colourless oil, 71%; ν_{max} (film)/cm^{-1} 2979, 2928, 2253, 1749, 1632, 1598, 1505, 1443, 1381, 1318, 1062, 1022; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.37–7.34 (m, 3H, *o*-Ar*H* and OC*H*CH), 7.29–7.22 (m, 3H, *m*- and *p*-Ar*H*), 6.33 (dd, *J* = 3.3, 1.8 Hz, 1H, OCHC*H*), 6.18 (dd, *J* = 3.1, 0.7 Hz, 1H, OCHCHC*H*), 4.53 (app. sext., *J* = 6.3 Hz, 1H, OC*H*CH_2), 3.21 (dd, *J* = 15.3, 6.2 Hz, 1H, OCHC*H*$_2$), 2.97 (dd, *J* = 15.3, 6.6 Hz, 1H, OCHC*H*$_2$), 1.46 (d, *J* = 6.3 Hz, 3H, C*H*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 150.9 (C_q), 141.9 (CH), 131.6 (CH), 128.3 (CH), 126.7 (CH), 124.2 (C_q), 110.6 (CH), 107.7 (CH), 97.0 (C_q), 83.7 (CH), 41.8 (C_q), 34.2 (CH_2), 19.2 (CH_3); LRMS (EI) 226 (22), 184 (15), 156 (7), 109 (100), 81 (42); HRMS (EI) calc'd for $C_{15}H_{14}O_2$ ($M+H^+$) 226.0988, found 226.0985.

2-(2-Methyl-2,3-dihydronaphtho[2,3-*b*]furan-4-yl)acetaldehyde 204

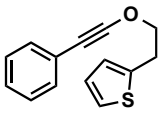


To a flask containing CH_2Cl_2 (10 mL) was added **203** (40 mg, 0.18 mmol, 1.0 eq), Ph_3PAuCl (4.5 mg, 0.009 mmol, 0.05 eq) and $AgBF_4$ (1.7 mg, 0.009 mmol, 0.05 eq). The solution was stirred at rt for 2 h, after which complete consumption of **203** was observed by TLC. The solvent was removed *in vacuo*, and the crude product purified *via* column chromatography (0–20% CH_2Cl_2/PE) to yield **204**.

Yellow oil, 24%; ν_{max} (film)/cm^{-1} 2925, 1719, 1633, 1439, 1380, 1237, 1169, 1085, 1019; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 9.74 (s, 1H, aldehyde), 7.78 (d, *J* = 8.1 Hz, 1H, **2**-Ar*H*), 7.72 (d, *J* = 8.1 Hz, 1H, **5**-Ar*H*), 7.42 (t, *J* = 7.3 Hz, 1H, **3**-Ar*H*), 7.35 (t, *J* = 8.0 Hz, 1H, **4**-Ar*H*), 7.07 (s, 1H, **1**-Ar*H*), 5.03 (sext., *J* = 6.8 Hz, 1H, OC*H*CH_3), 4.05 (br s, 2H, (C)C*H*$_2$CO), 3.46 (dd, *J* = 15.8, 8.4 Hz, 1H, (C)C*H*$_2$CH), 2.94 (dd, *J* = 15.8,

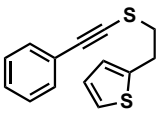
7.2 Hz, 1H, (C)CH_2CH), 1.54 (d, J = 6.2 Hz, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 198.4 (CH), 157.7 (C_q), 135.3 (C_q), 131.1 (C_q), 128.3 (C_q), 127.9 (CH), 126.0 (CH), 124.2 (C_q), 123.9 (CH), 123.1 (CH), 104.0 (CH), 79.8 (CH), 45.3 (CH_2), 36.5 (CH_2), 22.0 (CH_3); LRMS (EI) 226 (96), 197 (100), 182 (16), 152 (20); HRMS (ESI) calc'd for $C_{15}H_{15}O_2$ ($M+H^+$) 227.1072, found 227.1071.

2-(2-((Phenylethynyl)oxy)ethyl)thiophene 207



Synthesised using 2-(thiophen-2-yl)ethan-1-ol, according to general procedure **J**. Colourless oil, 50%; ν_{max} (film)/cm^{-1} 2950, 2255, 1728, 1598, 1491, 1461, 1440, 1423, 1320, 1056; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.37 (d, J = 7.7 Hz, 2H, *o*-Ar*H*), 7.28 (t, J = 7.5 Hz, 2H, *m*-Ar*H*), 7.25 (m, 1H, *p*-Ar*H*), 7.22 (d, J = 5.0 Hz, 1H, SC*H*), 6.99 (t, J = 4.0 Hz, 1H, SCHC*H*), 6.95 (m, 1H, S(C)C*H*), 4.36 (t, J = 6.8 Hz, 2H, OCH_2), 3.36 (t, J = 6.8 Hz, 2H, OCH$_2$CH_2); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 138.6 (C_q), 131.7 (CH), 128.3 (CH), 127.2 (CH), 126.9 (CH), 126.2 (CH), 124.5 (CH), 123.8 (C_q), 98.3 (C_q), 78.6 (CH_2), 40.5 (C_q), 29.5 (CH_2); LRMS (EI) 228 (15), 111 (100); HRMS (EI) calc'd for $C_{14}H_{12}OS$ (M^+) 228.0603, found 228.0603.

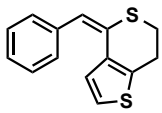
2-(2-((Phenylethynyl)thio)ethyl)thiophene 209



Synthesised using 2-(thiophen-2-yl)ethane-1-thiol, according to general procedure **F**. Yellow oil, 67%; ν_{max} (film)/cm^{-1} 3059, 2918, 2163, 1593, 1484, 1438, 1319, 1282, 1237, 1172, 1107, 1068; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.46–7.44 (m, 2H, *o*-Ar*H*), 7.34–7.31 (m, 3H, *m*- and *p*-Ar*H*), 7.19 (dd, J = 5.1, 1.1 Hz, 1H, SC*H*), 6.97 (dd, J = 5.1, 3.5 Hz, 1H, SCHC*H*), 6.93 (dd, J = 3.5, 1.1 Hz, 1H, S(C)C*H*), 3.36 (t, J = 7.7 Hz, 2H, SCH_2), 3.07 (t, J = 7.7 Hz, 2H, SCH$_2$CH_2); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 141.9 (C_q), 131.7 (CH), 128.5 (CH), 128.4 (CH), 127.1 (CH), 125.6 (CH), 124.2 (CH), 123.4

(C_q), 94.0 (C_q), 78.7 (C_q), 37.0 (CH_2), 30.0 (CH_2); LRMS (EI) 244 (100), 211 (23), 197 (9), 134 (32), 111 (84); HRMS (EI) calc'd for $C_{14}H_{12}S_2$ (M^+) 244.0375, found 244.0358.

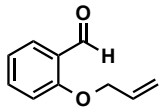
(*E*)-4-Benzylidene-6,7-dihydro-4*H*-thieno[3,2-*c*]thiopyran 210



In a flame-dried sealed tube under an atmosphere of argon was added $FeCl_3$ (9.3 mg, 0.06 mmol, 1.0 eq), **209** (14 mg, 0.06 mmol, 1.0 eq) and chlorobenzene (2 mL). The mixture was stirred at rt for 30 min, then gently heated to 50 °C and stirred for 2 h. The temperature was increased further to 70 °C, and the mixture stirred for a further 1 h, after which complete consumption of **209** was observed by TLC. The crude material was filtered through a layer of Celite® and purified *via* column chromatography (0 – 5% EtOAc/PE) to yield **210**.

Pale yellow oil, 44%; ν_{max} (film)/cm^{-1} 2917, 2848, 1661, 1581, 1507, 1489, 1441, 1419, 1275, 1245, 1074; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.59 (d, J = 7.6 Hz, 2H, *o*-Ar*H*), 7.40–7.37 (m, 3H, *m*-Ar*H* and SC*H*), 7.24 (t, J = 7.4 Hz, 1H, *p*-Ar*H*), 7.11 (d, J = 5.4 Hz, 1H, SCHC*H*), 7.05 (s, 1H, PhC*H*), 3.21 (t, J = 6.1 Hz, 2H, SCH_2), 3.03 (t, J = 6.1 Hz, 2H, SCH_2CH_2); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 137.0 (C_q), 136.7 (C_q), 132.9 (C_q), 129.4 (CH), 128.5 (C_q), 128.3 (CH), 128.8 (CH), 124.3 (CH), 122.2 (CH), 121.4 (CH), 27.4 (CH_2), 26.8 (CH_2); LRMS (CI) 245 (100), 155 (2); HRMS (CI) calc'd for $C_{14}H_{12}S_2$ (M^+) 244.0375, found 244.0378.

2-(Allyloxy)benzaldehyde 214

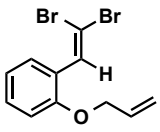


In a flask open to air, salicylaldehyde (3.44 g, 28.2 mmol, 1.0 eq) and allyl bromide (3.65 mL, 42.3 mmol, 1.5 eq) were stirred in DMF (15 mL). Potassium carbonate (5.83

g, 42.3 mmol, 1.5 eq) was added as a single portion, and the bright yellow mixture stirred at rt for 1 h. The reaction was diluted with water (100 mL) and the organic portion extracted with Et_2O (3 x 50 mL). The organic portions were combined and washed with brine (50 mL). The organic layer was dried over Na_2SO_4, filtered, concentrated *in vacuo* and purified *via* column chromatography (0–5% EtOAc/PE) to yield **214**.

Colourless oil, >99%; ν_{max} (film)/cm^{-1} 2862, 1682, 1597, 1481, 1454, 1395, 1283, 1188, 1160, 1102; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 10.55 (s, 1H, aldehyde), 7.85 (dd, *J* = 7.7, 1.8 Hz, 1H, CO(C)C*H*), 7.53 (td, *J* = 7.9, 1.9 Hz, 1H, O(C)CHC*H*), 7.04 (tt, *J* = 7.4, 0.9 Hz, 1H, CO(C)CHC*H*), 6.98 (d, *J* = 8.4 Hz, 1H, O(C)C*H*), 6.08 (m, 1H, OCH_2CH), 5.46 (dq, *J* = 17.3, 1.7 Hz, 1H, *E*-OCH_2CHCH), 5.34 (dq, *J* = 10.6, 1.4 Hz, 1H, *Z*-OCH_2CHCH), 4.67 (dt, *J* = 5.2, 1.5 Hz, 2H, OCH_2); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 189.9 (CH), 161.1 (C_q), 135.9 (CH), 132.5 (CH), 128.6 (CH), 125.3 (C_q), 121.0 (CH), 118.2 (CH_2), 113.0 (CH), 69.3 (CH_2); LRMS (CI) 180 (100), 163 (36). Data in agreement with literature values.[ii]

1-(Allyloxy)-2-(2,2-dibromovinyl)benzene 215

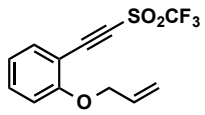


In a flame-dried flask flushed with argon, PPh_3 (9.7 g, 37.0 mmol, 4.0 eq) was dissolved in CH_2Cl_2, and cooled to 0 °C. Carbon tetrabromide (6.1 g, 18.5 mmol, 2.0 eq) was added, and the solution stirred at 0 °C for 15 min. **214** dissolved in CH_2Cl_2 (10 mL) was added dropwise over 30 s, after which the mixture was warmed to rt and stirred for 30 min. Petroleum ether 40–60 °C (50 mL) was added as a single portion to give a brown slurry, which was stirred at rt for a further 15 min, then filtered under suction. The crude product was purified *via* column chromatography (0–2% EtOAc/PE) to yield **215**.

[ii] Law, K. R.; McErlean, C. S. P., *Chem. Eur. J.*, **2013**, *47*, 15852

Yellow oil, 94%; ν_{max} (film)/cm^{-1} 3074, 3024, 2916, 1596, 1579, 1482, 1448, 1422, 1290, 1241, 1224, 1107; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.71 (dd, *J* = 7.7, 1.8 Hz, 1H, O(C)(C)C*H*), 7.64 (s, 1H, C*H*CBr_2), 7.30 (td, *J* = 7.9, 1.7 Hz, 1H, O(C)CHC*H*), 6.97 (td, *J* = 7.6, 1.1 Hz, 1H, O(C)CHCHC*H*), 6.87 (dd, *J* = 8.3, 0.9 Hz, 1H, O(C)C*H*), 6.06 (m, 1H, OCH_2C*H*), 5.42 (dq, *J* = 17.2, 1.7 Hz, 1H, OCH_2CHCH_2), 5.31 (dq, *J* = 10.7, 1.7 Hz, 1H, OCH_2CHCH_2), 4.57 (dt, *J* = 5.1, 1.6 Hz, 2H, OCH_2); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 155.7 (C_q), 133.1 (CH), 133.0 (CH), 129.9 (CH), 129.3 (CH), 124.8 (C_q), 120.5 (CH), 117.7 (CH_2), 112.0 (CH), 89.8 (C_q), 69.2 (CH_2); LRMS (EI) 320 (17), 318 (34), 316 (17), 279 (6), 277 (12), 275 (6), 198 (95), 196 (100), 158 (62).
Data in agreement with literature values.[jj]

1-(Allyloxy)-2-(((trifluoromethyl)sulfonyl)ethynyl)benzene 217



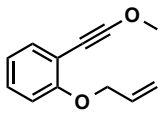
A flask containing **215** (2.75 g, 8.65 mmol, 1.0 eq) was flushed with argon, diluted with THF (20 mL) and cooled to –78 °C. ^{n}BuLi (2.5 M in hexanes, 7.6 mL, 19.0 mmol, 2.2 eq) was added dropwise *via* syringe, and the mixture stirred for 1 h at –78 °C. Trifluoromethanesulfonic anhydride (1.60 mL, 9.52 mmol, 1.1 eq) was added dropwise, and the reaction stirred for 30 min at –78 °C. The crude mixture was quenched by addition of saturated NH_4Cl solution (10 mL). The organic portion was extracted with CH_2Cl_2 (50 mL), then washed with water (20 mL) and brine (20 mL), and dried over $MgSO_4$. Filtration, concentration and purification *via* column chromatography (0–5% EtOAc/PE) yielded **217**.

Yellow oil, 40%; ν_{max} (film)/cm^{-1} 2872, 2171, 1596, 1574, 1488, 1449, 1375, 1289, 1265, 1210, 1165, 1111; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.59 (dd, *J* = 7.7, 1.8 Hz, 1H, O(C)(C)C*H*), 7.54 (td, *J* = 8.2, 1.7 Hz, 1H, O(C)CHC*H*), 7.02 (t, *J* = 7.5 Hz, 1H, O(C)CHCHC*H*), 6.95 (d, *J* = 8.6 Hz, 1H, O(C)C*H*), 6.06–6.00 (m, 1H, OCH_2C*H*), 5.48 (dd, *J* = 17.5, 1.6 Hz, 1H, OCH_2CHCH_2), 5.35 (dd, *J* = 10.7, 1.6 Hz, 1H,

[jj] Li, Y.; Jardine, K. J.; Tan, R.; Song, D.; Dong, V. M., *Angew. Chem. Int. Ed.,* **2009**, *48*, 9690

OCH_2CHCH), 4.65 (dt, J = 4.9, 1.6 Hz, 2H, OCH_2); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 162.2 (C_q), 135.3 (CH), 135.2 (CH), 131.8 (CH), 121.1 (CH),120.3 and 118.1 (C_q, J = 326 Hz), 118.2 (CH_2), 112.6 (CH), 105.8 (C_q), 99.3 (C_q), 81.1 (C_q), 69.5 (CH_2); LRMS (EI) 290 (42), 181 (7), 157 (40), 128 (100), 115 (12); HRMS (EI) calc'd for $C_{12}H_9F_3O_3S$ (M^+) 290.0219, found 290.0218.

1-(Allyloxy)-2-(methoxyethynyl)benzene 211

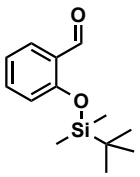


Synthesised using **217** and methanol, according to general procedure **J**.

Pale yellow oil, 42%; ν_{max} (film)/cm^{-1} 3077, 2948, 2267, 1729, 1598, 1488, 1450, 1353, 1326, 1272, 1226, 1163, 1119; ^1H NMR (600 MHz, $CDCl_3$) δ_H 7.33 (dd, J = 7.6, 1.8 Hz, 1H, O(C)(C)CH), 7.17 (td, J = 7.7, 1.7 Hz, 1H, O(C)CHCH), 6.87 (td, J = 7.5, 1.1 Hz, 1H, O(C)CHCHCH), 6.84 (d, J = 8.3 Hz, 1H, O(C)CH), 6.12–6.06 (m, 1H, OCH_2CH), 5.49 (dq, J = 17.2, 1.7 Hz, 1H, OCH_2CHCH), 5.29 (dq, J = 10.6, 1.7 Hz, 1H, OCH_2CHCH), 4.60 (dt, J = 4.9, 1.6 Hz, 2H, OCH_2), 4.02 (s, 3H, OCH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 158.9 (C_q), 133.5 (2 x CH) *, 127.9 (CH), 120.8 (CH), 117.2 (CH_2), 113.6 (C_q), 112.6 (CH), 104.1 (C_q), 69.4 (CH_2), 66.1 (CH_3), 35.0 (C_q); LRMS (EI) 188 (57), 173 (26), 161 (100), 145 (51), 128 (41), 115 (56), 104 (53); HRMS (EI) calc'd for $C_{12}H_{12}O_2$ (M^+) 188.0832, found 118.0831.

* 2 overlapping peaks

2-((*tert*-Butyldimethylsilyl)oxy)benzaldehyde 220a

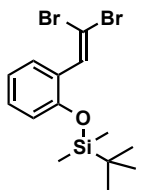


TBDSCl (5.92 g, 39.9 mmol, 1.2 eq.) was dissolved in CH_2Cl_2 (40 mL), and added dropwise over 10 minutes to a solution of salicylaldehyde (4.00 g, 32.8 mmol, 1.0 eq.), DMAP (64.0 mg, 0.52 mmol, 0.016 eq.) and triethylamine (3.98 g, 39.9 mmol, 1.2

eq.) in CH_2Cl_2 (80 mL) at 0 °C. The solution was allowed to warm to rt, and stirred for a further 90 min. The reaction was quenched by addition of saturated $NaHCO_3$ solution (20 mL). The organic layer was separated, and the aqueous extracted with CH_2Cl_2 (3 x 50 mL). The organic portions were combined and washed with brine (50 mL) and dried over $MgSO_4$. Filtration, concentration *in vacuo* and purification *via* column chromatography (0–10% EtOAc/PE) yielded **220a**.

Colourless oil, 78%; ν_{max} (film)/cm^{-1} 2955, 2931, 2858, 1688, 1598, 1478, 1457, 1389, 1306, 1251, 914; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 10.47 (s, 1H, C*H*O), 7.81 (dd, *J* = 7.7, 1.8 Hz, 1H, CO(C)C*H*), 7.46 (td, *J* = 7.9, 1.9 Hz, 1H, O(C)CHC*H*), 7.03 (t, *J* = 7.4 Hz, 1H, O(C)CHCHC*H*), 6.88 (d, *J* = 8.4 Hz, 1H, O(C)C*H*), 1.02 (s, 9H, Si(C)(CH_3)$_3$), 0.28 (s, 6H, 2 x SiCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 190.3 (C_q), 159.1 (C_q), 135.8 (CH), 128.5 (CH), 127.4 (C_q), 121.6 (CH), 120.4 (CH), 25.8 (CH_3), 18.5 (C_q), –4.2 (CH_3); LRMS (CI) 237 (100), 221 (18), 179 (8), 86 (13), 59 (19).
Data in agreement with literature values[kk].

***tert*-Butyl(2-(2,2-dibromovinyl)phenoxy)dimethylsilane 220b**

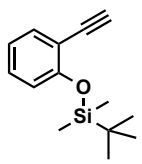


In a flame dried flask flushed with argon, triphenylphosphine (26.7 g, 102 mmol, 4.0 eq.) was dissolved in CH_2Cl_2 (80 mL) and cooled to 0 °C. To the cooled solution was added a solution of carbon tetrabromide (16.9 g, 51.0 mmol, 2.0 eq.) in CH_2Cl_2 (10 mL). The mixture was stirred at 0 °C for 15 min, then aldehyde **220a** (6.00 g, 25.4 mmol, 1.0 eq.) dissolved in CH_2Cl_2 (10 mL) was added dropwise over 30 s. The solution was allowed to warm to rt and stirred for a further 30 min. To the mixture was added petroleum ether (100 mL), and the resulting brown precipitate was stirred for a further 15 min at rt. The precipitate was filtered to remove solid, and the filtrate purified *via* column chromatography (2% EtOAc/PE) to yield **220b**.

[kk] Lewis, R. S.; Garza, C. J.; Dang, A. T.; Pedro, T. K. A.; Chain, W. J., *Org. Lett.* **2015**, 2278

Pale yellow oil, 82%; ν_{max} (film)/cm^{-1} 2955, 2929, 2858, 1596, 1572, 1477, 1449, 1282, 1250, 1102, 916; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.65 (dd, *J* = 7.7, 1.6 Hz, 1H, O(C)(C)C*H*), 7.58 (s, 1H, C*H*CBr_2), 7.23 (dt, *J* = 7.8, 1.8 Hz, 1H, O(C)CHC*H*), 6.98 (t, *J* = 7.6 Hz, 1H, O(C)CHCHC*H*), 6.82 (dd, *J* = 8.2, 1.0 Hz, 1H, O(C)C*H*), 1.03 (s, 9H, Si(C)(CH_3)$_3$), 0.21 (s, 6H, 2 x SiCH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 153.2 (C_q), 134.2 (CH), 129.9 (CH), 129.4 (CH), 127.5 (C_q), 121.2 (CH), 119.6 (CH), 89.9 (C_q), 25.8 (CH_3), 18.4 (C_q), -4.3 (CH_3); LRMS (EI) 394 (16), 392 (32), 390 (16), 337 (57), 335 (100), 333 (52), 257 (16), 256 (88), 255 (36), 254 (89), 253 (20), 241 (57), 239 (51), 203 (4), 175 (10), 159 (6), 139 (24), 137 (23);
Data in agreement with literature values[ll]

tert-Butyl(2-ethynylphenoxy)dimethylsilane 220c



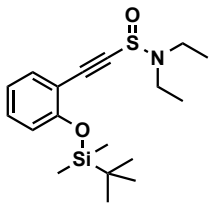
To a flame dried flask flushed with argon was added **220b** (8.10 g, 20.8 mmol, 1.0 eq.) and THF (50 mL). The mixture was cooled to –78 °C. To the solution was added dropwise *n*BuLi (2.5 M in hexanes, 18.0 mL, 2.2 eq.). The solution was stirred at –78 °C for 30 min, then quenched by addition of saturated NH_4Cl solution (10 mL). The organic solvent was removed *in vacuo*, and the aqueous component was extracted with EtOAc (3 x 50 mL). The organic portions were combined, washed with brine and dried over $MgSO_4$. Purification *via* column chromatography (100% PE) yielded **220c**.

Pale yellow oil, 90%; ν_{max} (film)/cm^{-1} 3316, 2956, 2930, 2858, 2108, 1595, 1568, 1484, 1444, 1286, 1251, 1102, 911; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.42 (dd, *J* = 7.7, 1.7 Hz, 1H, O(C)(C)C*H*), 7.22 (td, *J* = 7.8, 1.8 Hz, 1H, O(C)CHC*H*), 6.91 (td, *J* = 7.5, 1.1 Hz, 1H, O(C)CHCHC*H*), 6.83 (dd, *J* = 8.2, 1.0 Hz, 1H, O(C)CH), 3.19 (s, 1H, alkyne C*H*), 1.04 (s, 9H, Si(C)(CH_3)$_3$), 0.24 (s, 6H, 2 x SiCH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 157.3 (C_q), 134.1 (CH), 130.1 (CH), 121.2 (CH), 120.0 (CH), 114.8 (C_q), 81.2 (CH), 81.0 (C_q), 25.9 (CH_3), 18.4 (C_q), –4.1 (CH_3); LRMS (CI) 233 (91), 217

[ll] Pearson, E. L.; Willis, A. C.; Sherburn, M. S.; Paddon-Row, M. N., *Org. Biomol. Chem.* **2008**, 513

(25), 177 (24), 175 (12), 125 (15), 111 (43), 97 (75), 85 (100); HRMS (CI) calc'd for $C_{14}H_{20}OSi$ (M^+) requires 233.1356, found 233.1355.

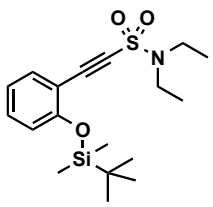
2-(2-((*tert*-Butyldimethylsilyl)oxy)phenyl)-*N*,*N*-diethylethyne-1-sulfinamide 220d



Synthesised from **220c**, according to general procedure **D**

Pale yellow oil, 96% (based on 43% recovered SM); ν_{max} (film)/cm^{-1} 2971, 2931, 2859, 2162, 1595, 1485, 1445, 1381, 1291, 1255, 1185, 1095; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.45 (dd, *J* = 7.7, 1.7 Hz, 1H, O(C)(C)C*H*), 7.29 (td, *J* = 7.7, 1.8 Hz, 1H, O(C)CHC*H*), 6.94 (td, *J* = 7.4, 1.0 Hz, 1H, O(C)CHCHC*H*), 6.84 (d, *J* = 8.3 Hz, 1H, O(C)C*H*), 3.39 (dq, *J* = 13.6, 7.1 Hz, 4H, 2 x NCH_2CH$_3$), 1.27 (t, *J* = 7.2 Hz, 6H, 2 x NCH$_2$CH_3), 1.03 (s, 9H, Si(C)(CH_3)$_3$), 0.25 (s, 6H, 2 x SiCH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 157.4 (C_q), 134.1 (CH), 131.7 (CH), 121.4 (CH), 119.9 (CH), 112.9 (C_q), 94.9 (C_q), 89.6 (C_q), 42.7 (CH_2), 25.8 (CH_3), 18.4 (C_q), 14.4 (CH_3), –4.15 (CH_3); LRMS (ESI) 352 (100); HRMS (ESI) calc'd for $C_{18}H_{30}NO_2SSi$ ($M+H^+$) requires 352.1767, found 352.1771.

2-(2-((*tert*-Butyldimethylsilyl)oxy)phenyl)-*N*,*N*-diethylethyne-1-sulfonamide 220

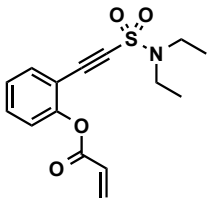


Synthesised from **220d**, according to general procedure **E**.

Colourless oil, 70%; ν_{max} (film)/cm^{-1} 2931, 2859, 2178, 1595, 1569, 1485, 1446, 1293, 1201, 1152, 1107, 1017; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.45 (dd, *J* = 7.8, 1.7 Hz, 1H,

O(C)(C)C*H*), 7.33 (td, *J* = 7.3, 1.8 Hz, 1H, O(C)CHC*H*), 6.95 (td, *J* = 7.6, 1.0 Hz, 1H, O(C)CHCHC*H*), 6.86 (dd, *J* = 8.4, 0.6 Hz, 1H, O(C)C*H*), 3.36 (q, *J* = 7.2 Hz, 4H, 2 x NC*H*$_2$CH$_3$), 1.29 (t, *J* = 7.2 Hz, 6H, 2 x NCH$_2$C*H*$_3$), 1.04 (s, 9H, Si(C)(C*H*$_3$)$_3$), 0.27 (s, 6H, 2 x SiC*H*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 158.1 (C_q), 134.5 (CH), 132.4 (CH), 121.4 (CH), 119.9 (CH), 111.4 (C_q), 87.0 (C_q), 86.5 (C_q), 43.1 (CH_2), 25.8 (CH_3), 18.4 (C_q), 13.8 (CH_3), –4.1 (CH_3); LRMS (ESI) 368 (100), 352 (72), 214 (10), 169 (12); HRMS (ESI) calc'd for $C_{18}H_{30}NO_3SSi$ ($M+H^+$) requires 368.1716, found 368.1718.

2-((*N*,*N*-Diethylsulfamoyl)ethynyl)phenyl acrylate 221

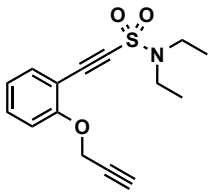


To a flame dried flask under an atmosphere of argon was added sulfonamide **220** (500 mg, 1.36 mmol, 1.0 eq.) and anhydrous THF (20 mL), and the solution was cooled to 0 °C. To the cooled solution was added *tert*-butyl ammonium fluoride (1.0 M in THF, 1.50 mmol, 1.1 eq.). The solution was stirred at 0 °C for a further 20 min, then quenched with NH_4Cl (10 mL). The organic portion was extracted with CH_2Cl_2 (3 x 50 mL), combined and washed with brine (50 mL). The organic solvent was removed *in vacuo*, then the crude reaction material redissolved in Et_2O (20 mL). Triethylamine (210 μL, 1.50 mmol, 1.1 eq) was added and the mixture stirred for 5 min at rt. Acrolyl chloride (150 mg, 1.63 mmol, 1.2 eq) was added dropwise to give a cloudy solution, which was stirred for a further 30 min at rt. The crude reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with water (50 mL) and brine (50 mL). The organic portion was dried over $MgSO_4$, filtered and concentrated *in vacuo*, then purified *via* column chromatography (0–10% EtOAc/PE) to give **221**.

Viscous, pale yellow oil, 83%; ν_{max} (film)/cm^{-1} 2979, 2186, 1748, 1631, 1602, 1573, 1485, 1447, 1404, 1359, 1294, 1235, 1136, 1068, 1016; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.60 (dd, *J* = 7.8, 1.6 Hz, 1H, O(C)(C)C*H*), 7.52 (td, *J* = 7.8, 1.7 Hz, 1H,

O(C)CHC*H*), 7.30 (td, *J* = 7.7, 1.1 Hz, 1H, O(C)CHCHC*H*), 7.24 (dd, *J* = 8.2, 0.9 Hz, 1H, O(C)C*H*), 6.69 (dd, *J* = 17.4, 1.1 Hz, 1H, *Z*-terminal alkene proton), 6.36 (dd, *J* = 17.4, 10.5 Hz, 1H, COC*H*), 6.11 (dd, *J* = 10.5, 1.1 Hz, *E*-terminal alkene proton), 3.31 (q, *J* = 7.2 Hz, 4H, 2 x NCH_2CH$_3$), 1.26 (t, *J* = 7.2 Hz, 6H, 2 x CH$_2$CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 163.6 (C_q), 152.4 (C_q), 134.1 (CH), 134.0 (CH_2), 132.3 (CH), 127.3 (CH), 126.3 (CH), 122.9 (CH), 113.2 (C_q), 88.2 (C_q), 83.3 (C_q), 43.2 (CH_2), 13.6 (CH_3); LRMS (ESI) 330 (98), 308 (100), 261 (15), 214 (65); HRMS (ESI) calc'd for $C_{15}H_{18}NO_4S$ ($M+H^+$) requires 308.0957, found 308.0944.

_N_,_N_-Diethyl-2-(2-(prop-2-yn-1-yloxy)phenyl)ethyne-1-sulfonamide 222



To a flame dried flask under an atmosphere of argon was added sulfonamide **220** (1.41 g, 3.84 mmol, 1.0 eq.) and anhydrous THF (30 mL), and the solution was cooled to 0 °C. To the cooled solution was added *tert*-butyl ammonium fluoride (1.0 M in THF, 4.22 mmol, 1.1 eq.). The solution was stirred at 0 °C for a further 20 min, then quenched with NH_4Cl (10 mL). The organic portion was extracted with CH_2Cl_2 (3 x 50 mL), combined and washed with brine (50 mL). The organic solvent was removed *in vacuo*, then the crude reaction material redissolved in acetone (20 mL). Potassium carbonate (795 mg, 5.78 mmol, 1.5 eq) and propargyl bromide (80% in toluene, 620 μL, 5.78 mmol, 1.5 eq) were added, and the mixture heated to reflux for 2 h. The crude reaction mixture was cooled to rt and quenched by addition of NH_4Cl (10 mL). The reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with water (50 mL) and brine (50 mL). The organic portion was dried over $MgSO_4$, filtered and concentrated *in vacuo*, then purified *via* column chromatography (0–20% EtOAc/PE) to give **222**.

Viscous, pale yellow oil, 60%; ν_{max} (film)/cm^{-1} 3282, 2978, 2179, 1596, 1575, 1487, 1448, 1354, 1340, 1149, 1114, 1067, 1014; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.50 (dd, *J* = 7.6, 1.8 Hz, 1H, O(C)(C)C*H*), 7.44 (td, *J* = 8.0, 1.8 Hz, 1H, O(C)CHC*H*), 7.04 (d,

J = 8.5 Hz, 1H, O(C)C*H*), 7.01 (td, *J* = 7.6, 0.9 Hz, 1H, O(C)CHCHC*H*), 4.76 (d, *J* = 2.3 Hz, 2H, OC*H*$_2$(C)), 3.40 (q, *J* = 7.2 Hz, 4H, 2 x NC*H*$_2$CH$_3$), 2.54 (t, *J* = 2.3 Hz, 1H, C*H*(C)CH$_2$), 1.31 (t, *J* = 7.2 Hz, 6H, 2 x NCH$_2$C*H*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 159.4 (C_q), 134.5 (CH), 132.4 (CH), 121.6 (CH), 112.5 (CH), 108.8 (C_q), 87.7 (C_q), 85.3 (C_q), 77.8 (C_q), 76.4 (CH), 56.5 (CH_2), 43.0 (CH_2), 13.4 (CH_3); LRMS (EI) 291 (32), 276 (37), 226 (19), 198 (22), 155 (97), 128 (100); HRMS (EI) calc'd for $C_{15}H_{17}O_3NS$ (M^+) 291.0924, found 291.0923.

11. References

1. Gomberg, M., *J. Am. Chem. Soc.*, **1900**, *22*, 757

2. van der Klerk, G. J. M.; Noltes, J. G.; Luijten, J. G. A., *J. Appl. Chem.*, **1957**, *7*, 356

3. Beckmann, E.; Paul, T., *Justus Liebigs Ann. Chim.*, **1891**, *266*, 1

4. Schlenk, W.; Weickel, T., *Ber. Dtsch. Chem. Ges.*, **1911**, *44*, 1182

5. Hou, Z.; Jia, X.; Fujita, A.; Tezuka, H.; Yamazaki, H.; Wakatsuki, Y., *Chem. Eur. J.*, **2000**, *6*, 2994

6. Eakin, M.; Martin, J.; Parker, W., *Chem. Commun.*, **1965**, *11*, 206

7. Birch, A. J., *J. Chem. Soc.*, **1944**, 430

8. Campbell, K. N.; Eby, L. T., *J. Am. Chem. Soc.*, **1941**, *63*, 216

9. Kornblum, N.; Michel, R. E.; Kerber, R. C., *J. Am. Chem. Soc.*, **1966**, *88*, 5660

10. Kornblum, N.; Michel, R. E.; Kerber, R. C., *J. Am. Chem. Soc.*, **1966**, *88*, 5662

11. Russell, G. A.; Danen, W. C., *J. Am. Chem. Soc.*, **1966**, *88*, 5663

12. Savéant, J. -M., *Adv. Phys. Org. Chem.*, **2000**, *35*, 117

13. Ashby, E. C.; Lopp, I. G.; Buhler, J. D., *J. Am. Chem. Soc.*, **1975**, *97*, 1964

14. Ashby, E. C.; Goel, A. B.; DePriest, R. N., *J. Org. Chem.*, **1981**, *46*, 2429

15. Ashby, E. C.; Argyropoulos, J. N., *J. Org. Chem.*, **1986**, *51*, 3593

16. Ashby, E. C., *Acc. Chem. Res.*, **1988**, *21*, 414

17. Pross, A., *Acc. Chem. Res.*, **1985**, *18*, 212

18. Barton, D. H. R.; Basu, N. K.; Hesse, R. H.; Morehouse, F. S.; Pechet, M. M., *J. Am. Chem. Soc.*, **1966**, *88*, 3016

19. Davies, D. T.; Kapur, N.; Parsons, A. F., *Tetrahedron Lett.*, **1999**, *40*, 8615

20. Ishibashi, H.; Nakamura, N.; Sato, T.; Takeuchi, M.; Ikeda, M., *Tetrahedron Lett.*, **1991**, *32*, 1725

21. Chiara, J. L.; Cabri, W.; Hanessian, S., *Tetrahedron Lett.*, **1991**, *32*, 1125

22. Markham, A.; Goa, K. L., *Drugs*, **1997**, *54*, 299

23. Sharpe, M.; Jarvis, B.; Goa, K. L., *Drugs*, **2001**, *61*, 1501

24. Deprez, P.; Guillaume, J.; Becker, R.; Corbier, A.; Didierlaurent, S.; Fortin, M.; Frechet, D.; Hamon, G.; Heckmann, B.; Heitsch, H.; Kleemann, H. -W.; Vevert, J. -P.; Vincent, J. -C.; Wagner, A.; Zhang, J., *J. Med. Chem.*, **1995**, *38*, 2357

25. Matheron, M. E.; Porchas, M., *Plant Disease*, **2004**, *88*, 665

26. Noyori, N.; Tomino, I.; Tanimoto, Y., *J. Am. Chem. Soc.*, **1979**, *101*, 3129
27. Ullmann, F.; Bielecki, J., *Chem. Ber.*, **1901**, *34*, 2174
28. Zhang, S.; Zhang, D.; Liebeskind, L. S., *J. Org. Chem.*, **1997**, *62*, 2312
29. Kharasch, M. S.; Hields, E. K., *J. Am. Chem. Soc.*, **1941**, *63*, 2316
30. Sekiya, A.; Ishikawa, N., *J. Organomet. Chem.*, **1976**, *118*, 349
31. Negishi, E. -i.; King, A. O.; Okukado, N., *J. Org. Chem.*, **1977**, *42*, 1821
32. Miyaura, N.; Suzuki, A., *J. Chem. Soc., Chem. Commun.*, **1979**, 866
33. Stille, J. K., *Angew. Chem. Int. Ed.*, **1986**, *25*, 508
34. http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2010/
35. Dasgupta, R.; Malti, B. R., *Ind. Eng. Chem. Process Des. Dev.*, **1986**, *25*, 381
36. Sargent, M. V.; Stransky, P. O., *J. Chem. Soc. Perkin Trans. 1*, **1982**, 1605
37. Ames, D. E.; Bull, D., *Tetrahedron*, **1982**, *38*, 383
38. Ames, D. E.; Opalko, A., *Synthesis*, **1983**, *39*, 234
39. Ames, D. E.; Opalko, A., *Tetrahedron*, **1984**, *40*, 1919
40. Lane, B. S.; Brown, M. A.; Sames, D., *J. Am. Chem. Soc.*, **2005**, *127*, 8050
41. Yanagisawa, S.; Sudo, T.; Noyori, R.; Itami, K., *J. Am. Chem. Soc.*, **2006**, *128*, 11748
42. Campeau,L. -C.; Fagnou, K., *Chem. Commun.*, **2006**, *12*, 1253
43. Lafrance, M.; Fagnou, K., *J. Am. Chem. Soc.*, **2006**, *128*, 16496
44. Fujita, K. -i.; Nonogawa, M.; Yamaguchi, R., *Chem. Commun.*, **2004**, *17*, 1926
45. Sun, C. L.; Shi, Z. -J., *Chem. Rev.*, **2014**, *114*, 9219
46. The seven proposed pathways are; 1) HAS type reactions, 2) radical cation pathway, 3) cationic pathway, 4) electrophilic aromatic substitution, 5) nucleophilic aromatic substitution, 6) benzyne pathway, 7) organocatalysis pathway
47. Williams, G. H.; *Homolytic Aromatic Substitution*; Pergamon Press Ltd.; Oxford, UK, 1960
48. Beckwith, A. L. J.; Bowry, V. W.; Bowman, W. R.; Mann, E.; Parr, J.; Storey, J. M. D., *Angew. Chem. Int. Ed.*, **2004**, *43*, 95
49. Bolton, R.; Williams, G. H., *Chem. Soc. Rev.*, **1986**, *15*, 261
50. DeTar, D. F.; Long, R. A. J.; Rendleman, J.; Bradley, J.; Duncan, P., *J. Am. Chem. Soc.*, **1966**, *89*, 4051
51. Curran, D. P.; Keller, A. I., *J. Am. Chem. Soc.*, **2006**, *128*, 13706; Bowman, W. R.; Storey, J. M. D., *Chem. Soc. Rev.*, **2007**, *36*, 1803

52. Martínez-Barrasa, V.; García de Viedma, A.; Burgos, C.; Alvarez-Builla, J., *Org. Lett.*, **2000**, *2*, 3933
53. Yanagisawa, S.; Ueda, K.; Taniguchi, T.; Itami, K., *Org. Lett.*, **2008**, *10*, 4673
54. Sun, C. -L.; Li, H.; Yu, D. -G.; Yu, M.; Zhou, X.; Lu, X. -Y.; Huang, K.; Zheng, S. -F.; Li, B. -J.; Shi, Z. -J., *Nature Chemistry*, **2010**, *2*, 1044
55. Shirakawa, E.; Itoh, K. -I.; Higashino, T.; Hayashi, T., *J. Am. Chem. Soc.*, **2010**, *132*, 15537
56. Liu, W.; Cao, H.; Zhang, H.; Zhang, H.; Chung, K. H.; He, C.; Wang, H.; Kwong, Y. F.; Lei, A., *J. Am. Chem. Soc.*, **2010**, *132*, 16737
57. Bunnett, J. F., *Acc. Chem. Res.*, **1978**, *11*, 413
58. Studer, A.; Curran, D. P., *Angew. Chem. Int. Ed.*, **2011**, *50*, 5018
59. Giese, B.; *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*, Pergamon Press Ltd.; Oxford, UK, 1986; p 218
60. Shirakawa, E.; Hayashi, T., *Chem. Lett.*, **2012**, *41*, 130
61. Liu, W.; Tian, F.; Wang, X.; Yu, H.; Bi, Y., *Chem. Commun.*, **2013**, *49*, 2983
62. Chen, W. -C.; Hsu, Y. -C.; Shih, W. -C.; Lee, C. -Y.; Chuang, W. -H.; Tsai, Y. -F.; Chen, P. P. -Y.; Ong, T. -G., *Chem. Commun.*, **2012**, *48*, 6702
63. Yong, G. -P.; She, W. -L.; Zhang, Y. -M.; Li, Y. -Z., *Chem. Commun.*, **2011**, *47*, 11766
64. Tanimoro, K.; Ueno, M.; Takeda, K.; Kirihata, M.; Tanimori, S., *J. Org. Chem.*, **2012**, *77*, 7844
65. Zhao, H.; Shen, J.; Guo, J.; Ye, R.; Zeng, H., *Chem. Commun.*, **2013**, *49*, 2323
66. Gao, Y.; Tang, P.; Zhou, H.; Zhang, W.; Yang, H.; Yan, N.; Hum G.; Mei, D.; Wang, J.; Ma, D., *Angew. Chem. Int. Ed.*, **2016**, *55*, 3124
67. Walden Jr, G. H.; Hammett, L. P.; Chapman, R. P., *J. Am. Chem. Soc.*, **1931**, *53*, 3908
68. Sun, C. -L.; Gu, Y. -F.; Wang, B.; Shi, Z. -J., *Chem. Eur. J.*, **2011**, *17*, 10844
69. Zhou, S.; Anderson, G. M.; Mondal, B.; Doni, E.; Ironmonger, V.; Kranz, M.; Tuttle, T.; Murphy, J. A., *Chem. Sci.*, **2014**, *5*, 476
70. Murphy, J. A.; Khan, T. A.; Zhou, S. -Z.; Thomson, D. W.; Mahesh, M., *Angew. Chem. Int. Ed.*, **2005**, *44*, 1356
71. Murphy, J. A.; Zhou, S. -Z.; Thomson, D. W.; Schoenebeck, F.; Mahesh, M.; Park, S. R.; Tuttle, T.; Berlouis, L. E. A., *Angew. Chem. Int. Ed.*, **2007**, *46*, 5178
72. Yi, H.; Jutand, A.; Lei, A., *Chem. Commun.*, **2015**, *51*, 545

73. Patil, M., *J. Org. Chem*., **2016**, *81*, 632
74. Bunnett, J. F., *Acc. Chem. Res.*, **1992**, *25*, 2
75. Wu, Y.; Wong, S. M.; Mao, F.; Chan, T. L.; Kwong, F. Y., *Org. Lett*., **2012**, *14*, 5306
76. Zhou, S.; Doni, E.; Anderson, G. M.; Kane, R. G.; MacDougall, S. W.; Ironmonger, V. M.; Tuttle, T.; Murphy, J. A., *J. Am. Chem. Soc.*, **2014**, *136*, 17818
77. Woodward, R. B.; Wendler, N. L.; Brutschy, F. J., *J. Am. Chem. Soc.*, **1945***, 67*, 1425
78. Wotiz, J. H.; Kleopfer, R. D.; Barelski, P. M.; Hinckley, C. C; Koster, D. F., *J. Org. Chem.*, **1972**, *37*, 1758
79. Wislicenus, J., *Liebigs Ann. Chem.*, **1878**, *192*, 106
80. Effenberger, F., *Angew. Chem. Int. Ed.*, **1969**, *8*, 295
81. Jung, M. E.; Cordova, J.; Murakami, M., *Org. Lett.*, **2009**, *11*, 3882
82. Shimasaki, T.; Konno, Y.; Tobisu, M.; Chatani, N., *Org. Lett.*, **2009**, *11*, 4890
83. Hayashi, T.; Katsuro, Y.; Kumada, M., *Tetrahedron Lett*., **1980**, *21*, 3915
84. Okada, A.; Ohshima, T.; Shibasaki, M., *Tetrahedron Lett*., **2001**, *42*, 8023
85. Aggarwal, V. K.; Daly, A. M., *Chem. Commun.*, **2002**, 2490
86. Donohoe, T. J.; Fishlock, L. P.; Lacr, A. R.; Procopiou, P. A., *Org. Lett.*, **2007**, *9*, 953
87. Müller, T. E.; Beller, M., *Chem. Rev.*, **1998**, *98*, 675
88. Fittig, R., *Chem. Ber.*, **1875**, *8*, 357
89. Kutscheroff, M., *Chem. Ber.*, **1884**, *17*, 13
90. Thomas, R. J.; Campbell, K. N.; Hennion, G. F., *J. Am. Chem. Soc.*, **1938**, *60*, 718
91. Hinton, H. D.; Nieuwland, J. A., *J. Am. Chem. Soc.*, **1930**, *52*, 2892
92. Killian, D. B.; Hennion, G. F.; Nieuwland, J. A., *J. Am. Chem. Soc.*, **1934**, *56*, 1384
93. Fukudam Y.; Utimoto, K., *J. Org. Chem.*, **1991**, *56*, 3729
94. Norman, R. O. C.; Parr, W. J. E.; Thomas, C. B., *J. Chem. Soc., Perkin Trans. 1*, **1976**, *18*, 1983
95. Mizushima, E.; Sato, K.; Hayashi, T.; Tanaka, M., *Angew. Chem. Int. Ed.*, **2002**, *41*, 4563
96. Halpern, J.; James, B. R.; Kemp, A. L. W., *J. Am. Chem. Soc.*, **1961**, *83*, 4097
97. Blum, J.; Huminer, H., *J. Mol. Catal.*, **1992**, *75*, 153

98. Tokunaga, M.; Wakatsuki, Y., *Angew. Chem. Int. Ed.*, **1998**, *37*, 2867
99. Casado, R.; Contel, M.; Laguna, M.; Romero, P.; Sanz, S., *J. Am. Chem. Soc.*, **2003**, *125*, 11925
100. Kondo, M.; Kochi, T.; Kakiuchi, F., *J. Am. Chem. Soc.*, **2011**, *133*, 32
101. Dang, Y.; Qu, S.; Wang, Z. -X.; Wang, X., *Organometallics*, **2013**, *32*, 2804
102. Lam, R. H.; Walker, D. B.; Tucker, M. H.; Gatus, M. R. D.; Bhadbhade, M.; Messerle, B. A., *Organometallics*, **2015**, *34*, 4312
103. Newcomb, M.; Le Tadic-Biadetti, M. -H.; Chestney, D. L.; Roberts, E. S.; Hollenberg, P. F., *J. Am. Chem. Soc.*, **1995**, *117*, 12085
104. Miller, S. I., *J. Am. Chem. Soc.*, **1956**, *78*, 6091
105. Truce, W. E.; Simms, J. A., *J. Am. Chem. Soc.*, **1956**, *78*, 2756
106. Bellucci, G.; Chiappe, C.; Lo Moro, G., *Synlett*, **1996**, *9*, 880
107. Tzalis, D.; Koradin, C.; Knochel, P., *Tetrahedron Lett.*, **1999**, *40*, 6193
108. Imahori, T.; Hori, C.; Kondo, Y., *Adv. Synth. Catal.*, **2004,** *346*, 1090
109. Miyachi, N.; Shibasaki, M., *J. Org. Chem.*, **1990**, *55*, 1975
110. Takeda, H.; Shimada, S.; Ohnishi, S.; Nakanishi, F.; Matsuda, H., *Tetrahedron Lett*., **1998**, *39*, 3701
111. Busi, E.; Capozzi, G.; Menichetti, S.; Nativi, C., *Synthesis*, **1992**, *7*, 643
112. Alazet, S.; Zimmer, L.; Billard, T., *Angew. Chem. Int. Ed.*, **2013**, *52*, 10814
113. Godoi, B.; Sperança, A.; Back, D. F.; Brandão, R.; Nogueira, C. W.; Zeni, G., *J. Org. Chem.*, **2009**, *74*, 3469
114. Hossain, M. S.; Schwan, A. L., *Org. Lett.*, **2011**, *13*, 5330
115. See section **4.2**
116. Kabanyane, S. T.; MaGee, D. I., *Can. J. Chem.*, **1992**, *70*, 2758
117. Riddell, N.; Tam, W., *J. Org. Chem.*, **2006**, *71*, 1934
118. Zheng, W.; Zheng, F.; Hong, Y.; Hu, L., *Heteroatom Chemistry*, **2012**, *23*, 105
119. Chen, C.; Chu, L.; Qing, F. -L., *J. Am. Chem. Soc.*, **2012**, *134*, 12454
120. Ferry, A.; Billard, T.; Bacqué, E.; Langlois, B. R., *J. Fluorine Chem.*, **2012**, *134*, 160
121. Shao, X.; Xu, C.; Lu, L.; Shen, Q., *J. Org. Chem.*, **2015**, *80*, 3012
122. Ziegler, G. R.; Welch, C. A.; Orzech, C. E.; Kikkawa, S.; Miller, S. I., *J. Am. Chem. Soc.*, **1963**, *85*, 1648
123. Braga, A. L.; Reckziegel, A.; Menezes, P. H.; Stefani, H. A., *Tetrahedron Lett.*, **1993**, *34*, 393

124. Braga, A. L.; Silveira, C. C.; Reckziegel, A.; Menezes, P. H., *Tetrahedron Lett.*, **1993**, *34*, 8041

125. Moyano, A.; Charbonnier, F.; Greene, A. E., *J. Org. Chem.*, **1987**, *52*, 2919

126. Ni, Z.; Wang, S.; Mao, H.; Pan, Y., *Tetrahedron Lett*., **2012**, *53*, 3907

127. Yang, Y.; Dong, W.; Guo, Y.; Rioux, R. M., *Green Chem.*, **2013**, *15*, 3170

128. Arisawa, M.; Fujimoto, K.; Morinaka, S.; Yamaguchi, M., *J. Am. Chem. Soc.*, **2005**, *127*, 12226

129. Knapp, K. M.; Goldfuss, B.; Knochel, P., *Chem. Eur. J.*, **2003**, *9*, 5259

130. Hilt, G.; Lüers, S.; Harms, K., *J. Org. Chem.*, **2004**, *69*, 624

131. Sauer, J.; Heldman, D. K.; Hetzenegger, J.; Krauthan, J.; Sichert, H.; Schuster, J., *Eur. J. Org. Chem.*, **1998**, *12*, 2885; Nakayama, J.; Yamaoka, S.; Nakanishi, T.; Hoshino, M., *J. Am. Chem. Soc.*, **1988***, 110*, 6598

132. Ding, S.; Jia, G.; Sun, J., *Angew. Chem. Int. Ed.*, **2014**, *53*, 1877

133. Savarin, C.; Srogl, J.; Liebeskind, L. S., *Org. Lett.*, **2001**, *3*, 91

134. Melzig, L.; Stemper, J.; Knochel, P., *Synthesis*, **2010**, *12*, 2085

135. Melzig, L.; Metzger, A.; Knochel, P., *Chem. Eur. J.*, **2011**, *17*, 2948

136. Yang, Z.; Chen, X.; Kong, W.; Xia, S.; Zheng, R.; Luo, F.; Zhu, G., *Org. Biomol. Chem.*, **2013**, *11*, 2175

137. Yu, W.; Jin, Z., *J. Am. Chem. Soc.*, **2000**, *122*, 9840

138. Spanka, C.; Schaumann, E., *Synlett*, **2014**, *25*, 2415

139. Müller, M.; Förster, W. -R.; Holst, A.; Kingma, A. J.; Schaumann, E.; Adiwidjaja, G., *Chem. Eur. J.*, **1996**, *2*, 949

140. Gray, V. J.; Slater, B.; Wilden, J. D., *Chem. Eur. J.*, **2012**, *18*, 15582

141. Shirakawa, E.; Itoh, K. -i.; Higashino, T.; Hayashi, T., *J. Am. Chem. Soc*., **2010**, *132*, 15537; Liu, W.; Cao, H.; Zhang, H.; Zhang, H.; Chung, K. H.; He, C.; Wang, H.; Kwong, F. Y.; Lei, A., *J. Am. Chem. Soc.*, **2010**, *132*, 16737; Sun, C. -L.; Li, H.; Yu, D. -G.; Yu, M.; Zhou, X.; Lu, X. -Y.; Huang, K.; Zheng, S. -F.; Li, B. -J.; Shi, Z. -J., *Nature Chemistry*, **2010**, *2*, 1044

142. Shirakawa, E.; Zhang, X.; Hayashi, T., *Angew. Chem. Int. Ed.*, **2011**, *50*, 4671

143. Sun, C. -L.; Gu, Y. -F.; Wang, B.; Shi, Z. -J., *Chem. Eur. J.*, **2011**, *17*, 10844

144. Cuthbertson, J.; Gray, V. J.; Wilden, J. D., *Chem. Commun*., **2014**, *50*, 2575

145. Sammes, P. G.; Yahioglu, G., *Chem. Soc. Rev.*, **1994**, *23*, 327

146. Cumper, C. W. N.; Redford, D. G.; Vogel, A. I., *J. Chem. Soc.*, **1962,** 1158

147. Benfey, O. T.; Mills, J. W., *J. Am. Chem. Soc.*, **1971**, *93*, 922

148. Schmidt, E.; Hourdakis, A.; Popov, A. I., *Inorg. Chim. Acta*, **1981**, *52*, 91
149. Steed, J. W.; Atwood, J. L., *Supramolecular Chemistry*, John Wiley & Sons, Chichester, UK, 2000, p.142
150. Kaim, W., *J. Am. Chem. Soc.*, **1982**, *104*, 3833
151. Irving, W.; Williams, R. J. P., *J. Chem. Soc.*, **1953**, 3192; Banks, C. V.; Bystroff, R. I., *J. Am. Chem. Soc.*, **1959**, *81*, 6153
152. Gray, P.; Williams, A., *Chem. Rev.*, **1959**, *59*, 239
153. Pollitt, R. J.; Saunders, B. C., *J. Chem. Soc.*, **1965**, 4615
154. Steed, J. W.; Atwood, J. L., *Supramolecular Chemistry*, John Wiley & Sons; Chichester, UK, 2000, p. 116
155. Lindsten, G.; Wennerström, O.; Thulin, B., *Acta. Chem. Scand. Ser. B*, **1986**, *40*, 545
156. Poonia, N. S.; Truter, M. R., *J. Chem. Soc., Dalton Trans.*, **1973**, *19*, 2062
157. Fontana, F.; Kolt, R. J.; Huang, Y. Q.; Wayner, D. D. M., *J. Org. Chem.*, **1994**, *59*, 4671
158. Gassman, P. G.; Benecke, H. P., *Tetrahedron Lett.*, **1969**, *14*, 1089
159. BajRacharya, G. B.; Daugulis, O., *Org. Lett.*, **2008**, *10*, 4625
160. Lucarini, M.; Mugnaini, V.; Pedulli, G. F.; Guerra, M., *J. Am. Chem. Soc.*, **2003**, *125*, 8318
161. Roman, D. S.; Takahashi, Y.; Charette, A. B., *Org. Lett.*, **2011**, *13*, 3242
162. Kalyanaraman, V.; Rao, C. N. R.; George, M. V., *J. Chem. Soc. B*, **1971**, 2406
163. Newkome, G. R.; Hager, D. C., *J. Org. Chem.*, **1982**, *47*, 599
164. Tang, R. -J.; He, Q.; Yang, L., *Chem. Commun.*, **2015**, *51*, 5925
165. Krusic, P. J.; Wasserman, E.; Parkinson, B. A.; Malone, B.; Holler Jr., E. R., *J. Am. Chem. Soc.*, **1991**, *113*, 6274
166. Vincent Gray, unpublished results, UCL
167. Julia, M.; Righini, A.; Uguen, D., *J. Chem. Soc., Perkin Trans. 1*, **1978**, 1646
168. Wan, Y.; Alterman, M.; Larhead, M.; Hallberg, A., *J. Org. Chem.*, **2002**, *67*, 6232
169. Das, J. P.; Roy, S., *J. Org. Chem.*, **2002**, *67*, 7861
170. Galli, C.; Gentili, P.; Guarnieri, A.; Rappoport, Z., *J. Org. Chem.*, **1996**, *61*, 8878
171. Galli, C.; Rappoport, Z., *Acc. Chem. Res.*, **2003**, *36*, 580
172. Cuthbertson, J.; Wilden, J. D., *Tetrahedron*, **2015**, *71*, 4385

173. Hansch, C.; Leo, A.; Taft, R. W., *Chem. Rev.*, **1991**, *91*, 165
174. Caramella, P.; Houk, K. N., *Tetrahedron Lett.*, **1981**, *22*, 819
175. Kondoh, A.; Takami, K.; Yorimitsu, H.; Oshima, K., *J. Org. Chem.*, **2005**, *70*, 6468
176. Lucht, B. L.; Mao, S. S. H.; Tilley, T. D., *J. Am. Chem. Soc.*, **1998**, *120*, 4354
177. Shibata, T.; Fujiwara, R.; Takano, D., *Synlett*, **2005**, *13*, 2062
178. Lian, J. -J.; Chen, P. -C.; Lin, Y. -P.; Ting, H. -C.; Liu, R. -S., *J. Am. Chem. Soc.*, **2006**, *128*, 11372
179. Kocsis, L. S.; Benedetti, E.; Brummond, K. M., *Org. Lett.*, **2012**, *14*, 4430
180. de Koning, C. B.; Rousseau, A. L.; van Otterlo, W. A. L., *Tetrahedron*, **2003**, *59*, 7
181. Mohamed, R. K.; Peterson, P. W.; Alabugin, I. V., *Chem. Rev.*, **2013**, *113*, 7089
182. Gray, V. J.; Cuthbertson, J.; Wilden, J. D., *J. Org. Chem.*, **2014**, *79*, 5869
183. Smorada, R. L.; Truce, W. E., *J. Org. Chem.*, **1979**, *44*, 3444
184. García Ruano, J. L.; Alemán, J.; Marzo, L.; Alvarado, C.; Tortosa, M.; Díaz-Tendero, S.; Fraile, A., *Chem. Eur. J.*, **2012**, *18*, 8414
185. García Ruano, J. L.; Alemán, J.; Marzo, L.; Alvarado, C.; Tortosa, M.; Díaz-Tendero, S.; Fraile, A., *Angew. Chem. Int. Ed.*, **2012**, *51*, 2712
186. Marzo, L.; Parra, A.; Frías, M.; Alemán, J.; García Ruano, J. L., *Eur. J. Org. Chem.*, **2013**, *20*, 4405
187. Baudin, J. -B.; Julia, S. A.; Wang, Y., *Bull. Soc. Chim. Fr.*, **1995**, *132*, 952
188. Ashby, E. C.; Goel, A. B.; Park, W. S., *Tetrahedron Lett.*, **1981**, *22*, 4209
189. Gray, V. J.; Salvadori, E.; Cuthbertson, J.; Kay, C. W. M.; Wilden, J. D., manuscript in preparation
190. Hoogenboom, R., *Angew. Chem. Int. Ed.*, **2010**, *49*, 3415
191. Watanabe, H.; Gay, R. L.; Hauser, C. R., *J. Org. Chem.*, **1968**, *33*, 900
192. Chowdhury, R. M.; Wilden, J. D., *Org. Biomol. Chem.*, **2015**, *13*, 5859
193. Zhang, W.; Ready, J. M., *Angew. Chem. Int. Ed.*, **2014**, *53*, 8980
194. Sosa, J. R.; Tudjarian, A. A.; Minehan, T. G., *Org. Lett.*, **2008**, *10*, 5091
195. Lopchuk, J. M.; Green, I. L.; Badenock, J. C.; Gribble, G. W., *Org. Lett.*, **2013**, *15*, 4485
196. McNulty, J.; Keskar, K.; Bordón, C.; Yolken, R.; Jones-Brando, L., *Chem. Commun.*, **2014**, *50*, 8904

197. Burja, A. M.; Banaigs, B.; Abou-Mansour, E.; Burgess, J. G.; Wright, P. C., *Tetrahedron*, **2001**, *57*, 9347
198. Pieniazek, S. N.; Houk, K. N., *Angew. Chem. Int. Ed.*, **2006,** *45*, 1442
199. Hashmi, A. S. K.; Pankajakshan, S.; Rudolph, M.; Enns, E.; Bander, T.; Rominger, F.; Frey, W., *Adv. Synth. Catal.*, **2009**, *351*, 2855
200. Snow, A. W.; Foos, E. E., *Synthesis*, **2003**, *4*, 509
201. Adams, R.; Baker, B. R.; Wearn, R. B., *J. Am. Chem. Soc.*, **1940**, *62*, 2204
202. Hattori, T.; Suzuki, T.; Hayashizaka, N.; Koike, N.; Miyano, S., *Bull. Chem. Soc. Jpn.*, **1993**, *66*, 3034
203. Khanolkar, A. D.; Lu, D.; Ibrahim, M.; Duclos Jr., R. I.; Thakur, G. A.; Malan Jr., T. P.; Porreca, F.; Veerappan, V.; Tian, X.; George, C.; Parrish, D. A.; Papahatjis, D. P.; Makriyannis, A., *J. Med. Chem.*, **2007**, *50*, 6493
204. Schramm, M. P.; Reddy, D. S.; Kozmin, S. A., *Angew. Chem. Int. Ed.*, **2001**, *40*, 4274
205. Clark, J. S.; Trevitt, G. P.; Boyall, D.; Stammen, B., *Chem. Commun.*, **1998**, *23*, 2629
206. Yi Luo, unpublished results, UCL
207. Álvarez-Bercedo, P.; Flores-Gaspar, A.; Correa, A.; Martin, R., *J. Am. Chem. Soc.*, **2010**, *132*, 466
208. Sadana, A. K.; Saini, R. K.; Billups, W. E., *Chem. Rev.*, **2003**, *103*, 1539